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(71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; 974 Centre Road, WR-1ST18,, Wilmington, DE 19807 (US).

(72) Inventors: JIN, Fuqiang; Apartment F9, 3120 Naamans Road, Wilmington, DE 19810 (US). CONFALONE, Pasquale, N.; 303 Centennial Circle, Greenville, DE 19807 (US).

(74) Agent: REINERT, Norbert, F.; Du Pont Pharmaceuticals Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

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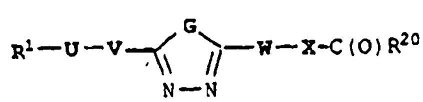
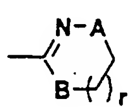
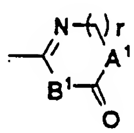
(54) Title: 1,3,4-THIADIAZOLES AND 1,3,4-OXADIAZOLES AS $\alpha_v\beta_3$ ANTAGONISTS



(I)



(a)



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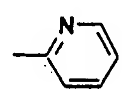

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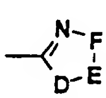

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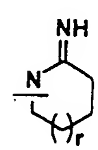
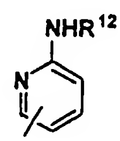
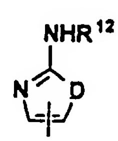


(e)



(f)



(g)

(57) Abstract

This invention relates to 1,3,4-thiadiazoles and 1,3,4-Oxadiazoles of formula (I), which are useful as antagonists of $\alpha_v\beta_3$ and related integrin receptors, to pharmaceutical compositions containing such compounds, alone or in combination with other therapeutic agents, for the inhibition of cell adhesion and the treatment of angioginic disorders, inflammation, bone degradation, tumors, metastases, thrombosis, and other cell aggregation-related conditions, including their enantiomeric, diastereomeric, pharmaceutically acceptable salt or prodrug forms thereof wherein R^1 is selected from formulas (a), (b), (c), (d), (e), (f) or (g); U, V, G, W, X, R^{20} are as defined in the application.

Title

1,3,4-Thiadiazoles and 1,3,4-Oxadiazoles as $\alpha_v\beta_3$ Antagonists

Field of the Invention

The present invention relates generally to 1,3,4-thiadiazoles and 1,3,4-Oxadiazoles which are useful as antagonists of the $\alpha_v\beta_3$ and related integrin receptors, to pharmaceutical compositions containing such compounds, processes for preparing such compounds, and to methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of cell adhesion and the treatment of angiogenic disorders, inflammation, bone degradation, tumors, metastases, thrombosis, and other cell aggregation-related conditions.

Background of the Invention

Angiogenesis or neovascularization is critical for normal physiological processes such as embryonic development and wound repair (Folkman and Shing, J. Biol. Chem. 1992, 267:10931-10934; D'Amore and Thompson, Ann. Rev. Physiol. 1987, 49:453-464). However, angiogenesis occurs pathologically, for example, in ocular neovascularization (leading to diabetic retinopathy, neovascular glaucoma, retinal vein occlusion and blindness), in rheumatoid arthitis and in solid tumors (Folkman and Shing, J. Biol. Chem., 1992, 267:10931-10934; Blood and Zetter, Biochim. Biophys. Acta., 1990, 1032:89-118).

Tumor dissemination, or metastasis, involves several distinct and complementary components, including the penetration and transversion of tumor cells through basement membranes and the establishment of self-sustaining tumor foci in diverse organ systems. To this end, the development and proliferation of new blood vessels, or angiogenesis, is critical to tumor

survival. Without neovascularization, tumor cells lack the nourishment to divide and will not be able to leave the primary tumor site (Folkman and Shing, J. Biol. Chem., 1992, 267:10931-10934).

Inhibition of angiogenesis in animal models of cancer has been shown to result in tumor growth suppression and prevention of metastatic growth. Many angiogenic inhibitors have been directed toward blocking initial cytokine-dependent induction of new vessel growth, e.g. antibodies to endothelial cell growth factors. However, these approaches are problematic because tumor and inflammatory cells can secrete multiple activators of angiogenesis (Brooks et al., Cell, 1994, 79:1157-1164). Therefore, a more general approach that would allow inhibition of angiogenesis due to a variety of stimuli would be of benefit.

The integrin $\alpha_v\beta_3$ is preferentially expressed on angiogenic blood vessels in chick and man (Brooks et al., Science, 1994, 264:569-571; Enenstein and Kramer, J. Invest. Dermatol., 1994, 103:381-386). Integrin $\alpha_v\beta_3$ is the most promiscuous member of the integrin family, allowing endothelial cells to interact with a wide variety of extracellular matrix components (Hynes, Cell, 1992, 69:11-25). These adhesive interactions are considered to be critical for angiogenesis since vascular cells must ultimately be capable of invading virtually all tissues.

While integrin $\alpha_v\beta_3$ promotes adhesive events important for angiogenesis, this receptor also transmits signals from the extracellular environment to the intracellular compartment (Leavesley et al., J. Cell Biol., 1993, 121:163-170, 1993). For example, the interaction between the $\alpha_v\beta_3$ integrin and extracellular matrix components promotes a calcium signal required for cell motility.

During endothelium injury, the basement membrane zones of blood vessels express several adhesive proteins, including but not limited to von Willebrand factor, fibronectin, and fibrin. Additionally, several members of the integrin family of adhesion receptors are expressed on the surface of endothelial, smooth muscle and on other circulating cells. Among these integrins is α_v/β_3, the endothelial cell, fibroblast, and smooth muscle cell receptor for adhesive proteins including von Willebrand factor, fibrinogen (fibrin), vitronectin, thrombospondin, and osteopontin. These integrins initiate a calcium-dependent signaling pathway that can lead to endothelial cell, smooth muscle cell migration and, therefore, may play a fundamental role in vascular cell biology.

Recently, an antibody to the $\alpha_v\beta_3$ integrin has been developed that inhibits the interaction of this integrin with agonists such as vitronectin (Brooks et al., Science, 1994, 264:569-571). Application of this antibody has been shown to disrupt ongoing angiogenesis on the chick chorioallantoic membrane (CAM), leading to rapid regression of histologically distinct human tumor transplanted onto the CAM (Brooks et al., Cell, 1994, 79:1157-1164). In this model, antagonists of the $\alpha_v\beta_3$ integrin induced apoptosis of the proliferating angiogenic vascular cells, leaving pre-existing quiescent blood vessels unaffected. Thus, $\alpha_v\beta_3$ integrin antagonists have been shown to inhibit angiogenesis. Based on this property, therapeutic utility of such agents is expected in human diseases such as cancer, rheumatoid arthritis and ocular vasculopathies (Folkman and Shing, J. Biol. Chem., 1992, 267:10931-10934).

Increasing numbers of other cell surface receptors have been identified which bind to extracellular matrix ligands or other cell adhesion ligands thereby mediating cell-cell and cell-matrix adhesion processes.

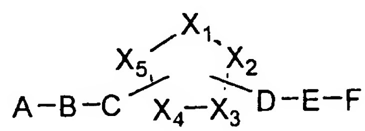
These receptors belong to a gene superfamily called integrins and are composed of heterodimeric transmembrane glycoproteins containing α- and β-subunits. Integrin subfamilies contain a common β-subunit combined with different α-subunits to form adhesion receptors with unique specificity. The genes for eight distinct β-subunits have been cloned and sequenced to date.

Two members of the β_1 subfamily, α_4/β_1 and α_5/β_1 have been implicated in various inflammatory processes. Antibodies to α_4 prevent adhesion of lymphocytes to synovial endothelial cells in vitro, a process which may be of importance in rheumatoid arthritis (VanDinther-Janssen et al., J. Immunol., 1991, 147:4207-4210). Additional studies with monoclonal anti-α_4 antibodies provide evidence that α_4/β_1 may additionally have a role in allergy, asthma, and autoimmune disorders (Walsh et al., J. Immunol., 1991, 146:3419; Bochner et al., J. Exp. Med., 1991 173:1553; Yednock et al., Nature, 1992, 356:63-66). Anti-α_4 antibodies also block the migration of leukocytes to the site of inflammation (Issedutz et al., J. Immunol., 1991, 147:4178-4184).

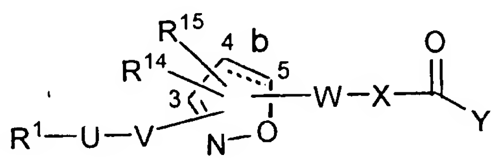
The α_v/β_3 heterodimer is a member of the β_3 integrin subfamily and has been described on platelets, endothelial cells, melanoma, smooth muscle cells, and osteoclasts (Horton and Davies, J. Bone Min. Res. 1989, 4:803-808; Davies et al., J. Cell. Biol. 1989, 109:1817-1826; Horton, Int. J. Exp. Pathol., 1990, 71:741-759). Like GPIIb/IIIa, the vitronectin receptor binds a variety of RGD-containing adhesive proteins such as vitronectin, fibronectin, VWF, fibrinogen, osteopontin, bone sialo protein II and thrombosponden in a manner mediated by the RGD sequence. A key event in bone resorption is the adhesion of osteoclasts to the matrix of bone. Studies with monoclonal antibodies have implicated the α_v/β_3 receptor in this process and

suggest that a selective α_v/β_3 antagonist would have utility in blocking bone resorption (Horton et al., J. Bone Miner. Res., 1993, 8:239-247; Helfrich et al., J. Bone Miner. Res., 1992, 7:335-343).

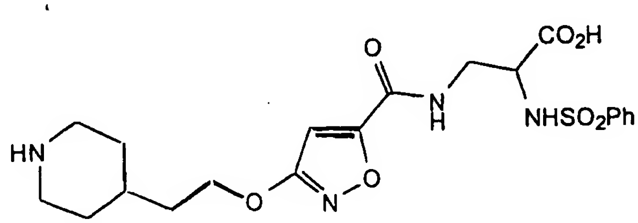
European Patent Application Publication Number 525629 (corresponds to Canadian Patent Application Publication Number 2,074,685) discloses compounds having the general formula:



Copending, commonly assigned U.S. Patent Application Serial Number 08/337,920 filed 11/10/94 discloses integrin inhibitors of the general formula shown below:

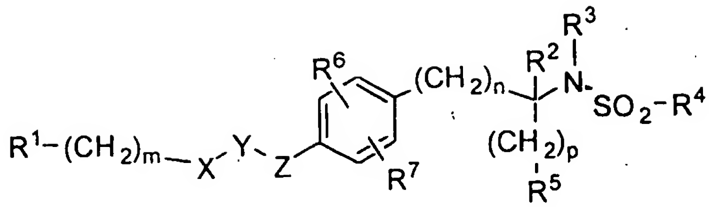


PCT Patent Application WO 94/08577 published 4/28/94 discloses fibrinogen antagonists, including the isoxazole-containing compound below:

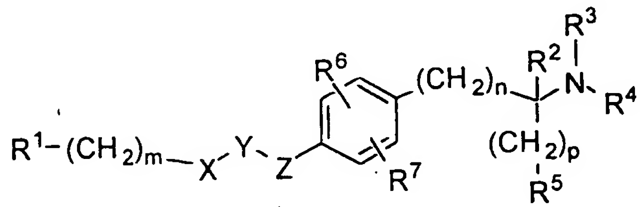


Several RGD-peptidomimetic compounds have been reported which block fibrinogen binding and prevent the formation of platelet thrombi.

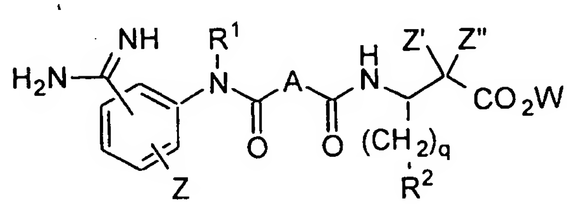
European Patent Application Publication Number 478363 relates to compounds having the general formula:



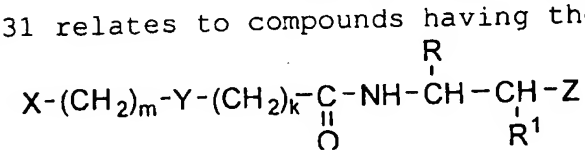
European Patent Application Publication Number 478328 relates to compounds having the general formula:



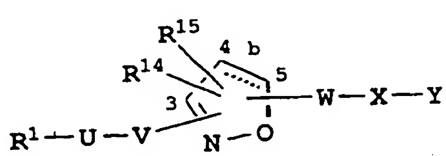
PCT Patent Application 9307867 relates to compounds having the general formula:



European Patent Application Publication Number 512831 relates to compounds having the general formula:



Copending commonly assigned US patent application USSN 08/455,768) (filed 5/31/95, Voss et al.) discloses compounds having the general formula:



which are useful as $\alpha_v\beta_3$ antagonists.

None of the above references teaches or suggests the compounds of the present invention which are described in detail below.

Summary of the Invention

The present invention provides novel nonpeptide compounds which bind to integrin receptors thereby altering cell-matrix and cell-cell adhesion processes. The compounds of the present invention are useful for the treatment of angiogenic disorders, inflammation, bone degradation, tumors, metastases, thrombosis, and other cell aggregation-related conditions in a mammal.

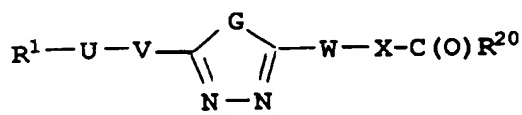
One aspect of this invention provides novel compounds of Formula I (described below) which are useful as antagonists of the α_v/β_3 or vitronectin receptor. The compounds of the present invention inhibit the binding of vironectin to α_v/β_3 and inhibit cell adhesion. The present invention also includes pharmaceutical compositions containing such compounds of Formula I, and methods of using such compounds for the inhibition of angiogenesis, and/or for the treatment of angiogenic disorders.

The present invention also provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment or prevention of diseases which involve cell adhesion processes, including, but not limited to, rheumatoid arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation, septic shock, psoriasis, eczema, contact dermatitis, osteoporosis, osteoarthritis, atherosclerosis, metastasis, wound healing, diabetic retinopathy, ocular vasculopathies, thrombosis, inflammatory bowel disease and other autoimmune diseases.

Also included in the present invention are pharmaceutical kits comprising one or more containers containing pharmaceutical dosage units comprising a compound of Formula I, for the treatment of cell adhesion related disorders, including, but not limited to, angiogenic disorders.

Detailed Description of the Invention

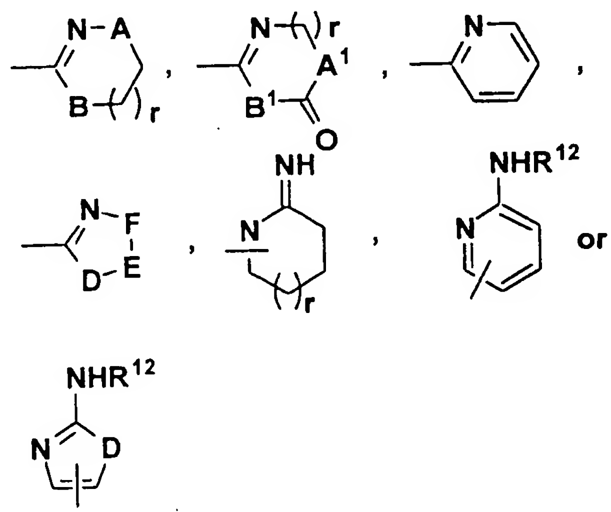
This invention relates to novel compounds of the Formula I:



(I)

including their enantiomeric, diastereomeric, pharmaceutically acceptable salt or prodrug forms thereof wherein:

R^1 is:



A and B are independently CH_2, O or $-N(R^{12})-$;

A^1 and B^1 are independently CH_2 or $-N(R^{10})-$;

D is NH, O, or S;

E-F is $-C(R^2)=C(R^3)-$, $-N=C(R^2)-$, $-C(R^2)=N-$, $-N=N-$, or $-CH(R^2)CH(R^3)-$;

G is selected from O or S;

R^2 and R^3 are independently selected from: H, C_1-C_4 alkoxy, $NR^{11}R^{12}$, $=NR^{12}$, halogen, NO_2, CN, CF_3, C_1-C_6

alkyl, C_3-C_6 alkenyl, C_3-C_7 cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, or C_7-C_{11} arylcarbonyl;

alternatively, R^2 and R^3 can be taken together to be a 5-7 membered carbocyclic or 5-7 membered heterocyclic ring system, said carbocyclic or heterocyclic ring being substituted with 0-2 R^7;

U is selected from:

$-(CH_2)_n-$,
$-(CH_2)_nN(R^{12})(CH_2)_m-$,
$-(CH_2)_nNHNH(CH_2)_m-$,
$-N(R^{10})C(=O)-$, or
$-C(=O)N(R^{10})-$;

V is selected from:

$-(CH_2)_n-$,
$-(C_1$-C_6 alkylene$)-Q-$, substituted with 0-3 groups independently selected from R^{13},
$-(C_2$-C_7 alkenylene$)-Q-$, substituted with 0-3 groups independently selected from R^{13},
$-(C_2$-C_7 alkynylene$)-Q-$, substituted with 0-3 groups independently selected from R^{13},
-(phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R^{13},
-(piperidinyl)-Q-, said piperidinyl substituted with 0-2 groups independently selected from R^{13},
-(pyridyl)-Q-, said pyridyl substituted with 0-2 groups independently selected from R^{13}, or
-(pyridazinyl)-Q-, said pyridazinyl substituted with 0-2 groups independently selected from R^{13} or R^7;

Q is selected from:

$-(CH_2)_n-$,
$-(CH_2)_nO(CH_2)_m-$,
$-(CH_2)_nN(R^{12})(CH_2)_m-$,
$-N(R^{10})C(=O)-$, or
$-C(=O)N(R^{10})-$;

W is selected from:
$-(CH_2)_qC(=O)N(R^{10})-$, $-SCH_2C(=O)N(R^{10})-$, or $-C(=O)-N(R^{10})-(CH_2)_q-$;

X is selected from:
$-(CH_2)_q-CH(R^8)-CH(R^9)-$, $-(CH_2)_q-CH(CH_2R^9)-$ or $-CH_2-$;

R^5 is selected from: H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_7-C_{14} bicycloalkyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, $-N(R^{11})R^{12}$; halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, morpholinyl or pyridinyl;

R^6 is selected from:
H, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, nitro, C_1-C_6 alkylcarbonyl, $-N(R^{11})R^{12}$, cyano, halo, $-S(O)mR^{10}$, CO_2R^{10}, OR^{10},
C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;
methylenedioxy when R^6 is a substituent on aryl,
or
a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, isoxazolinyl, isoxazolyl, or morpholinyl;

R^7 is selected from:
H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{11})R^{12}$, cyano, halo, CO_2R^{10}, OR^{10};

R^8 is selected from:
$CONR^{10}R^{11}$, $-CO_2R^{10}$,
C_1-C_{10} alkyl, substituted with 0-3 R^6,

C_2-C_{10} alkenyl, substituted with 0-3 R^6, C_2-C_{10} alkynyl, substituted with 0-3 R^6, C_3-C_8 cycloalkyl, substituted with 0-3 R^6, C_5-C_6 cycloalkenyl, substituted with 0-3 R^6, aryl, substituted with 0-3 R^6, a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, isoxazolinyl, isoxazolyl or morpholinyl;

R^9 is selected from: H, hydroxy, C_1-C_{10} alkoxy, nitro, $N(R^{10})R^{11}$, $-N(R^{16})R^{17}$, C_1-C_{10} alkyl substituted with 0-3 R^6, aryl substituted with 0-3 R^6, heteroaryl substituted with 0-3 R^6 or C_1-C_{10} alkylcarbonyl;

R^{10} is selected from H or C_1-C_{10} alkyl substituted with 0-2 R^5;

R^{11} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_3-C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantylmethyl, or C_1-C_{10} alkyl substituted with 0-2 R^5;

alternatively, R^{10} and R^{11} when both are substituents on the same nitrogen atom (as in $-NR^{10}R^{11}$) can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from: 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl; said heterocycle being optionally substituted with 1-3 groups selected from: C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6

alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_7-C_{11} arylalkoxycarbonyl, C_1-C_6 alkylsulfonyl or C_6-C_{10} arylsulfonyl;

R^{12} is selected from:

H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylsulfonyl, aryl(C_1-C_4 alkyl)sulfonyl, arylsulfonyl, aryl, heteroarylcarbonyl, or heteroarylalkylcarbonyl, wherein said aryl groups are substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{13} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^{10} or $-C(=O)N(R^{10})R^{11}$;

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,

$-C(=O)-R^{18b}$,

$-SO_2-R^{18a}$,

$-SO_2-N(18^{b})_2$;

R^{17} is selected from H or C_1-C_4 alkyl;

R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},

C_2-C_8 alkenyl substituted with 0-2 R^{19},

C_2-C_8 alkynyl substituted with 0-2 R^{19},

C_3-C_8 cycloalkyl substituted with 0-2 R^{19},

aryl substituted with 0-4 R^{19},

aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, isoxazolyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said

heterocyclic ring being substituted with 0-4 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, isoxazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from: H, halogen, CF_3, CN, NO_2, $NR^{11}R^{12}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

R^{20} is selected from:

hydroxy;

C_1 to C_{10} alkoxy;

methylcarbonyloxymethoxy-,

ethylcarbonyloxymethoxy-,

t-butylcarbonyloxymethoxy-,

cyclohexylcarbonyloxymethoxy-,

1-(methylcarbonyloxy)ethoxy-,

1-(ethylcarbonyloxy)ethoxy-,

1-(t-butylcarbonyloxy)ethoxy-,

1-(cyclohexylcarbonyloxy)ethoxy-,

i-propyloxycarbonyloxymethoxy-,

t-butyloxycarbonyloxymethoxy-,

1-(i-propyloxycarbonyloxy)ethoxy-,

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1-(*t*-butyloxycarbonyloxy)ethoxy-,

dimethylaminoethoxy-,

diethylaminoethoxy-,

(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-,
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-,
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-,
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-,

R^{21} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11}, cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^5;

m is 0-2;
n is 0-2;
p is 0-2;
q is 0-1; and
r is 0-2;

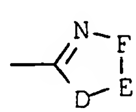
with the following provisos:

(1) n, m and q are chosen such that the number of atoms connecting R^1 and Y is in the range of 8-14; and

(2) when V is -(phenyl)-Q-, then either: U is not a direct bond (i.e., U is not $-(CH_2)_n-$ where n = 0) or Q is not a direct bond (i.e., Q is not $-(CH_2)_n-$ where n = 0).

A preferred embodiment of the invention are compounds of formula (I) as defined above wherein

R^1



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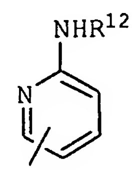
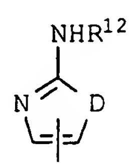


or



; and

V is selected from:

$-(CH_2)_n-$,

$-(C_1-C_6$ alkylene$)-Q-$, substituted with 0-3 groups independently selected from R^{13},

$-(C_2-C_7$ alkenylene$)-Q-$, substituted with 0-3 groups independently selected from R^{13},

$-(C_2-C_7$ alkynylene$)-Q-$, substituted with 0-3 groups independently selected from R^{13},

-(phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R^{13},

-(pyridyl)-Q-, said pyridyl substituted with 0-2 groups independently selected from R^{13}, or

-(pyridazinyl)-Q-, said pyridazinyl substituted with 0-2 groups independently selected from R^{13} or R^7;

The most preferred compounds of the invention are:

2(S)-Phenylsulfonylamino-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acetyl]aminopropionic acid

2(S)-(3-methylphenylsulfonyl)amino-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acetyl]aminopropionic acid

2(S)-Benzyloxycarbonylamino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-(2,4,6-Trimethylphenylsulfonyl)amino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-(1-Naphthalenesulfonyl)amino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-Benzyloxycarbonylamino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-(2,4,6-Trimethylphenylsulfonyl)amino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-(1-Naphthalenesulfonyl)amino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

In the present invention it has been discovered that the compounds of Formula I above are useful as inhibitors of cell-matrix and cell-cell adhesion processes. The present invention includes novel compounds of Formula I and methods for using such compounds for the prevention or treatment of diseases resulting from abnormal cell adhesion to the extracellular matrix which comprises administering to a host in need of such treatment a therapeutically effective amount of such compound of Formula I.

In the present invention it has also been discovered that the compounds of Formula I above are useful as inhibitors of $\alpha_v\beta_3$. The compounds of the present invention inhibit the binding of vitronectin to $\alpha_v\beta_3$ and inhibit cell adhesion.

The present invention also provides pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable carrier.

The compounds of Formula I of the present invention are useful for the treatment (including prevention) of angiogenic disorders. The term "angiogenic disorders" as used herein includes conditions involving abnormal neovascularization, such as tumor metastasis and ocular neovascularization, including, for example, diabetic retinopathy,

neovascular glaucoma, age-related macular degeneration, and retinal vein occlusion, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I described above.

The compounds of Formula I of the present invention may be useful for the treatment or prevention of other diseases which involve cell adhesion processes, including, but not limited to, inflammation, bone degradation, thromboembolic disorders, restenosis, rheumatoid arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation rejection, septic shock, psoriasis, eczema, contact dermatitis, osteoporosis, osteoarthritis, atherosclerosis, inflammatory bowel disease and other autoimmune diseases. The compounds of Formula I of the present invention may also be useful for wound healing.

The term "thromboembolic disorders" as used herein includes conditions involving platelet activation and aggregation, such as arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, thrombosis, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, myocardial infarction, cerebral embolism, kidney embolisms, pulmonary embolisms, or such disorders associated with diabetes, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I described above.

The compounds of the present invention may be used for other *ex vivo* applications to prevent cellular adhesion in biological samples.

Other applications of these compounds include prevention of platelet thrombosis, thromboembolism, and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty of coronary and other arteries and after coronary artery bypass procedures. The compounds of the present invention may also be used to prevent myocardial infarction. The compounds of the present invention are useful as thrombolytics for the treatment of thromboembolic disorders.

The compounds of the present invention can also be administered in combination with one or more additional therapeutic agents select from: anti-coagulant or coagulation inhibitory agents, such as heparin or warfarin; anti-platelet or platelet inhibitory agents, such as aspirin, piroxicam, or ticlopidine; thrombin inhibitors such as boropeptides, hirudin or argatroban; or thrombolytic or fibrinolytic agents, such as plasminogen activators, anistreplase, urokinase, or streptokinase.

The compounds of Formula I of the present invention can be administered in combination with one or more of the foregoing additional therapeutic agents, thereby to reduce the doses of each drug required to achieve the desired therapeutic effect. Thus, the combination treatment of the present invention permits the use of lower doses of each component, with reduced adverse, toxic effects of each component. A lower dosage minimizes the potential of side effects of the compounds, thereby providing an increased margin of safety relative to the margin of safety for each component when used as a single agent. Such combination therapies may be employed to achieve synergistic or additive therapeutic effects for the treatment of thromboembolic disorders.

By "therapeutically effective amount" it is meant an amount of a compound of Formula I that when

administered alone or in combination with an additional therapeutic agent to a cell or mammal is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

The term anti-coagulant agents (or coagulation inhibitory agents), as used herein, denotes agents that inhibit blood coagulation. Such agents include warfarin (available as Coumadin™) and heparin.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam. Piroxicam is commercially available from Pfizer Inc. (New York, NY), as Feldane™. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include thromboxane-A2-receptor antagonists and

thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The phrase thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin and other inhibitors of thrombin synthesis such as Factor XA. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. Such inhibitors include boroarginine derivatives and boropeptides, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boropeptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471 651 A2, the disclosures of which are hereby incorporated herein by reference, in their entirety.

The phrase thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator,

anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. Tissue plasminogen activator (tPA) is commercially available from Genentech Inc., South San Francisco, California. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosures of which are hereby incorporated herein by reference herein, in their entirety. Anistreplase is commercially available as Eminase^{TM}. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the binding of nitronection or fibrinogen to $\alpha_v\beta_3$. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving $\alpha_v\beta_3$. The compounds of the present invention may also be used in diagnostic assays involving $\alpha_v\beta_3$.

The compounds herein described may have asymmetric centers. Unless otherwise indicated, all chiral, diastereomeric and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. It will be appreciated that compounds of the present

invention that contain asymmetrically substituted carbon atoms may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

When any variable (for example but not limited to, R^2, R^4, R^6, R^7, R^8, R^{12},and R^{14}, n, etc.) occurs more than one time in any constituent or in any formula, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^4, then said group may optionally be substituted with up to two R^4 and R^4 at each occurrence is selected independently from the defined list of possible R^4. Also, by way of example, for the group $-N(R^{5a})_2$, each of the two R^{5a} substituents on N is independently selected from the defined list of possible R^{5a}. Similarly, by way of example, for the group $-C(R^7)_2-$, each of the two R^7 substituents on C is independently selected from the defined list of possible R^7.

When a bond to a substituent is shown to cross the bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a bond joining a substituent to another group is not specifically shown or the atom in such other group to which the bond joins is not specifically shown, then such substituent may form a bond with any atom on such other group.

When a substituent is listed without indicating the atom *via* which such substituent is bonded to the rest of the compound of Formula I, then such substituent may be bonded *via* any atom in such

substituent. For example, when the substituent is piperazinyl or piperidinyl unless specified otherwise, said piperazinyl or piperidinyl group may be bonded to the rest of the compound of Formula I *via* any atom in such piperazinyl or piperidinyl group.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By stable compound or stable structure it is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "substituted", as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (for example, "C_1-C_{10}" denotes alkyl having 1 to 10 carbon atoms); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi-, or poly-cyclic ring systems, such as cyclopropyl, and cyclobutyl; cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl; and "bicycloalkyl" is intended to include saturated bicyclic ring groups such as [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, and so forth. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the

chain, such as ethenyl, propenyl and the like; and "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like.

The terms "alkylene", "alkenylene", "phenylene", and the like, refer to alkyl, alkenyl, and phenyl groups, respectively, which are connected by two bonds to the rest of the structure of Formula I. Such "alkylene", "alkenylene", "phenylene", and the like, may alternatively and equivalently be denoted herein as "-(alkyl)-", "-(alkenyl)-" and "-(phenyl)-", and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate and the like.

As used herein, "aryl" or "aromatic residue" is intended to mean phenyl or naphthyl optionally substituted with 0-3 groups independently selected from methyl, methoxy, amino, hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; the term "arylalkyl" represents an aryl group attached through an alkyl bridge.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 14-membered bicyclic or tricyclic or an up to 26-membered polycyclic carbon ring, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocyles include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, biphenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which may be saturated, partially unsaturated, or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, isoxazolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl, azocinyl, triazinyl, 6*H*-1,2,5-thiadiazinyl, 2*H*,6*H*-1,5,2-dithiazinyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, 1*H*-indazolyl, purinyl, 4*H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazole, carbazole, ß-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl,

phenarsazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl or oxazolidinyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "heteroaryl" refers to aromatic heterocyclic groups. Such heteroaryl groups are preferably 5-6 membered monocylic groups or 8-10 membered fused bicyclic groups. Examples of such heteroaryl groups include, but are not limited to pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothienyl, benzimidazolyl, quinolinyl, or isoquinolinyl.

As used herein, the term "chiral amine" refers to any amine containing compound that also contains a chiral center. Such compounds include, by way of example and without limitation, either enantiomer of cinchonidine, ephedrine, 2-phenylglycinol, 2-amino-3-methoxy-1-propanol, quinidine and pseudoephedrine.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound of Formula I is modified by making acid or base salts of the compound of Formula I. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of Formula I are prepared by modifying

functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of Formula I wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula I, and the like. Examples of the prodrug forms of the compounds of the present invention include the following esters:

methyl, ethyl, isopropyl, methylcarbonyloxymethyl-, ethylcarbonyloxymethyl-, t-butylcarbonyloxymethyl-, cyclohexylcarbonyloxymethyl-, 1-(methylcarbonyloxy)ethyl-, 1-(ethylcarbonyloxy)ethyl-, 1-(t-butylcarbonyloxy)ethyl-, 1-(cyclohexylcarbonyloxy)ethyl-, i-propyloxycarbonyloxymethyl-, cyclohexylcarbonyloxymethyl-, t-butyloxycarbonyloxymethyl-, 1-(i-propyloxycarbonyloxy)ethyl-, 1-(cyclohexyloxycarbonyloxy)ethyl-, 1-(t-butyloxycarbonyloxy)ethyl-, dimethylaminoethyl-, diethylaminoethyl-, (5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methyl-, (5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methyl-, (1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methyl-, 1-(2-(2-methoxypropyl)-carbonyloxy)ethyl-.

The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-

toxic salts or the quaternary ammonium salts of the compounds of Formula I formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammoinum hydroxide and the like.

As discussed above, pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid, respectively, in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate,

ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

The disclosures of all of the references cited herein are hereby incorporated herein by reference in their entirety.

Synthesis

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The following abbreviations are used herein:

Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
Cbz	benzyloxycarbonyl
DEC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
EtOAc	ethyl acetate
EtOH	ethyl alcohol

PLE	Pig liver esterase
pyr	pyridine
TBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

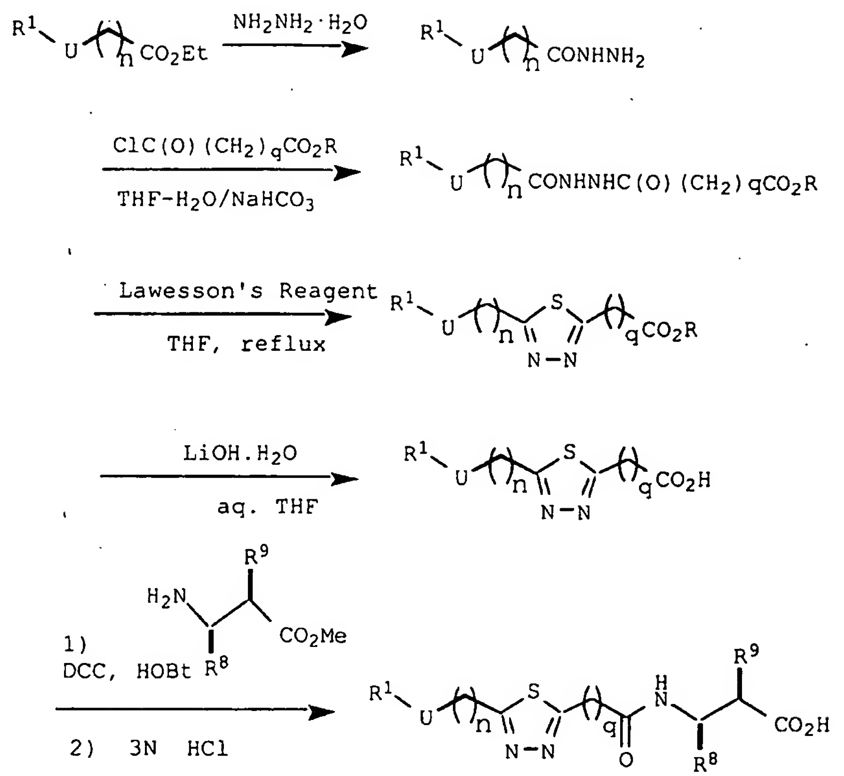
Compounds of Formula I wherein the central heterocycle is a 1,3,4-thiadiazole ring can be conveniently prepared by cyclization of N,N'-diacylhydrazine in the presence of Lawessen reagent(M. P. Cava, et al, Tetrahedron Lett. 1985, **41**, 5061) or P_2S_5(stelle, et al, J. Prakt. Chem 1904, **69**, 145).

Scheme I illustrates one synthetic sequence which will provide the 1,3,4-thiadiazoles of this invention. An appropriately substituted ester is treated with hydrazine monohydrate to afford the hydrazide which is then converted to N,N'-diacylhydrazine on reaction with an acid chloride in aqueous THF using NaHCO3 as base. The N,N'-diacylhydrazine thus obtained is then cyclized to afford the 1,3,4-thiadiazole.

Subsequent hydrolysis of the ester using conventional methods known to one skilled in the art of organic synthesis gives the desired acid. Coupling of the resulting acid to appropriately substituted α- or β-amino esters affords an intermediate which can be deprotected to give compounds of Formula I. The coupling is carried out using any of the many methods for the formation of amide bonds known to one skilled in the art of organic synthesis. These methods include but are not limited to conversion of the acid to the corresponding acid chloride, or use of standard coupling procedures such as the azide method, mixed carbonic acid anhydride (isobutyl chloroformate) method, carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimides) method, active ester (p-nitrophenyl

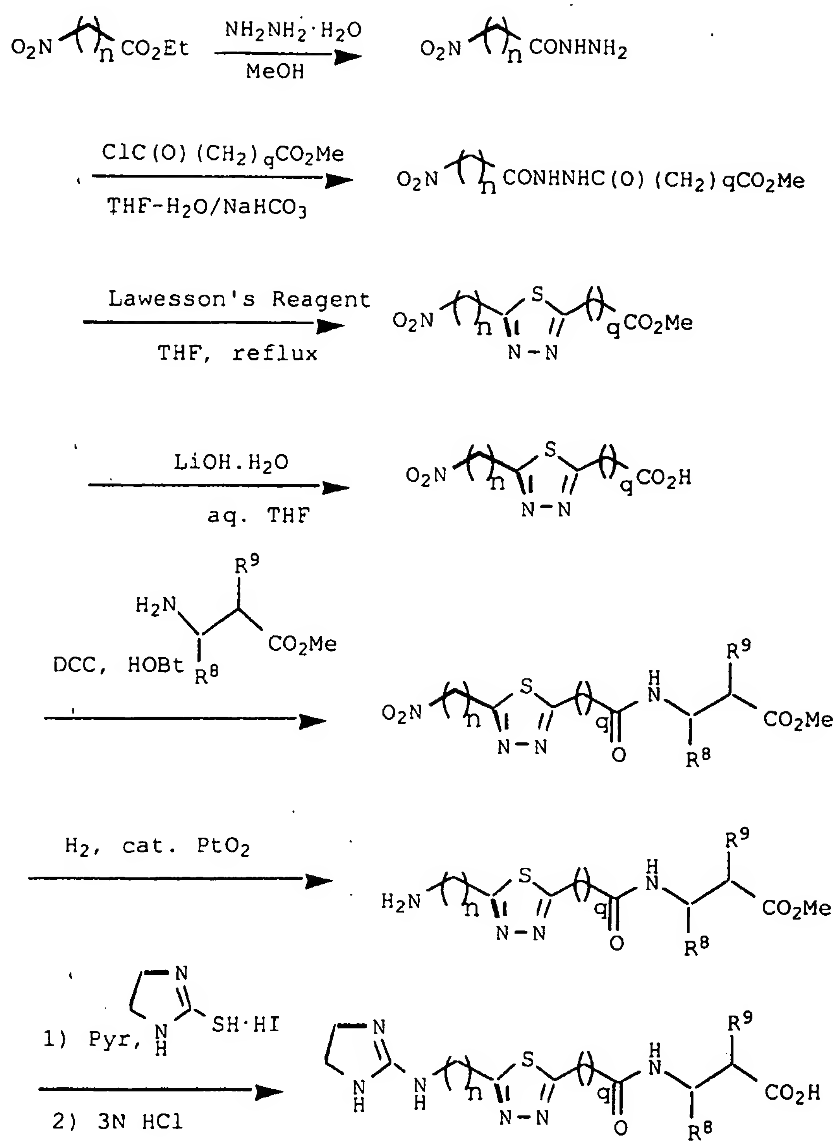
ester, N-hydroxysuccinic imido ester) method, carbonyldiimidazole method, phosphorus reagents such as BOP-Cl. Some of these methods (especially the carbodiimide) can be enhanced by the addition of 1-hydroxybenzotriazole.

Scheme I

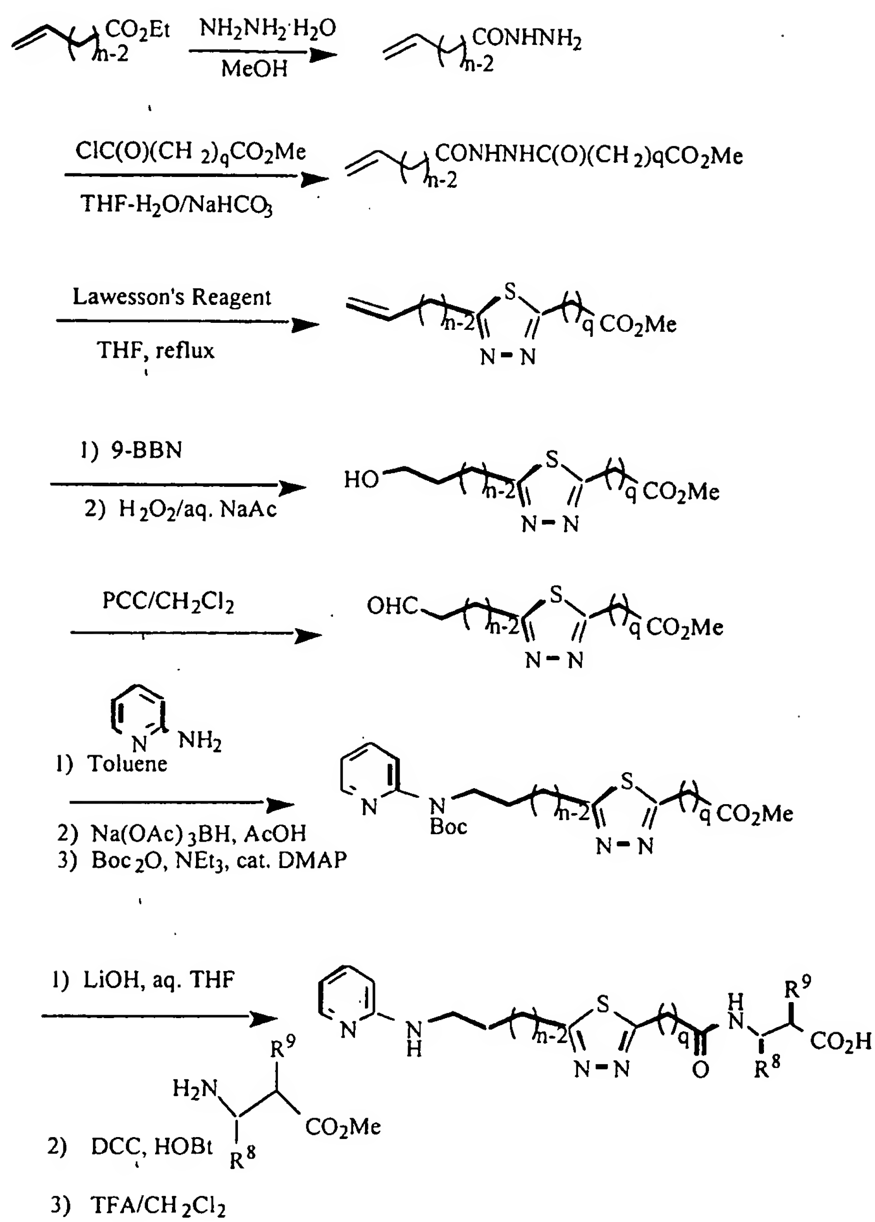


Alternately, as depicted in Scheme Ia and Ib, the above sequence can be carried out on an ester bearing a suitable functional group or protected functional group which can be converted into R^1 at a suitable stage of the synthesis of the target molecules.

Scheme Ia


O_2N CO_2Et
$NH_2NH_2 \cdot H_2O$
MeOH
O_2N $CONHNH_2$
$ClC(O)(CH_2)_qCO_2Me$
$THF-H_2O/NaHCO_3$
O_2N $CONHNHC(O)(CH_2)qCO_2Me$
Lawesson's Reagent
THF, reflux
CO_2Me
$LiOH.H_2O$
aq. THF
CO_2H
DCC, HOBt
H_2N
R^9
R^8
H_2, cat. PtO_2
1) Pyr,
SH·HI
2) 3N HCl

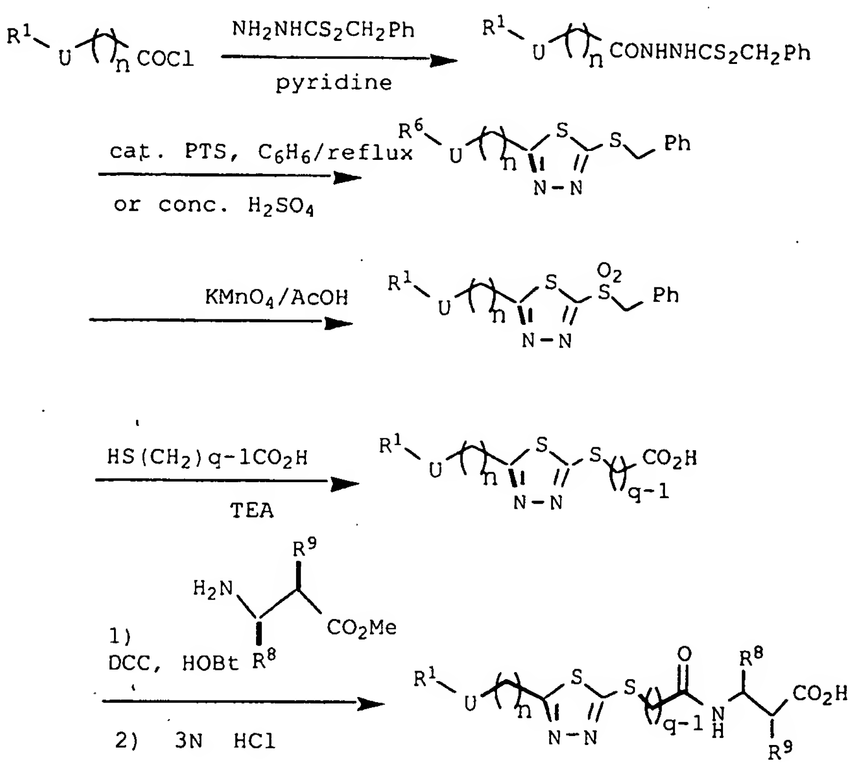
Scheme Ib



Additional 1,3,4-thiadiazolyl acids useful as starting materials for the preparation of compounds of Formula I, wherein W is $-SCH_2C(=O)N(R^{10})-$ can be prepared by substitution of a suitably substituted 1,3,4-thiadiazolyl sulfone with an acid thiol as shown in Scheme Ic using literature methods or modifications

thereof. (Fujii et al, J. Pharm. Soc. Japan 1954, 74, 1056; Young et al, J. Am. Chem. Soc. 1955, 77, 400).

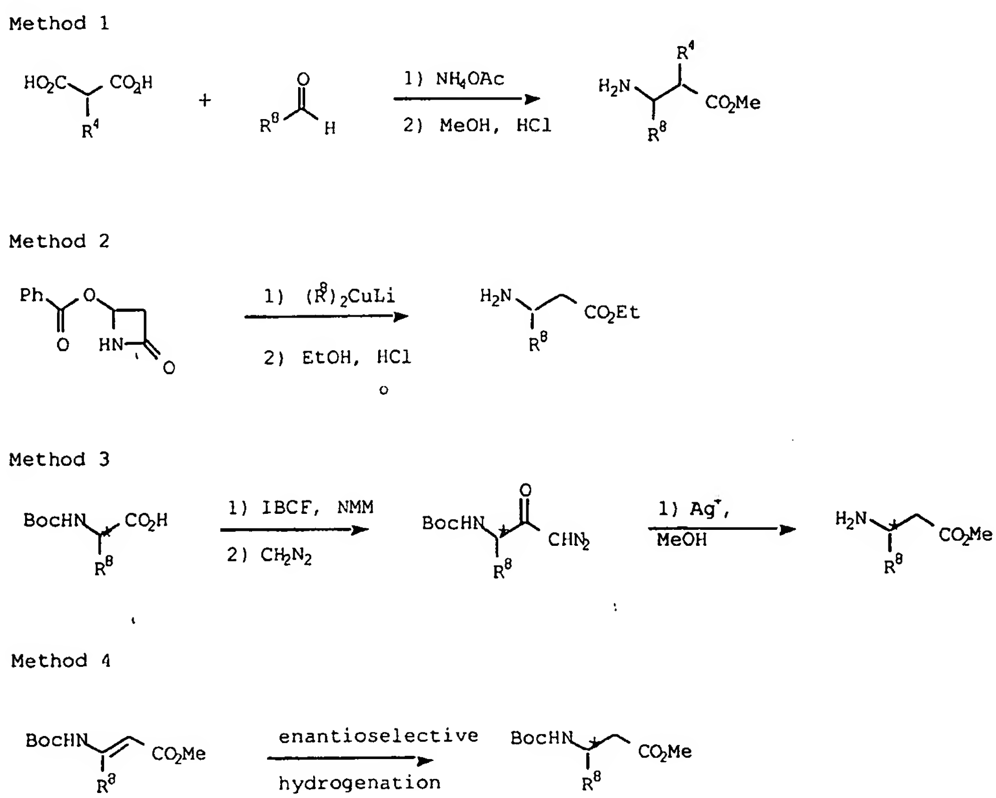
Scheme Ic



The appropriately substituted racemic b-amino acids may be purchased commercially or, as is shown in Scheme II, Method 1, prepared from the appropriate aldehyde, malonic acid and ammonium acetate according to the procedure of Johnson and Livak (J. Am. Chem. Soc. 1936, 58, 299). Racemic b-substituted-b-amino esters may be prepared through the reaction of dialkylcuprates or alkyllithiums with 4-benzoyloxy-2-azetidinone followed by treatment with anhydrous ethanol (Scheme I, Method 2) or by reductive amination of b-keto esters as is described in WO9316038. (Also see Rico et al., J. Org. Chem. 1993, 58, 7948-51.) Enantiomerically pure b-substituted-b-amino acids can be obtained through the optical resolution of the

racemic mixture or can be prepared using numerous methods, including: Arndt-Eistert homologation of the corresponding a-amino acids as shown in Scheme II, Method 3 (see Meier, and Zeller, Angew, Chem. Int. Ed. Engl. 1975, 14, 32; Rodriguez, et al. Tetrahedron Lett. 1990, 31, 5153; Greenlee, J. Med. Chem. 1985, 28, 434 and references cited within); and through an enantioselective hydrogenation of a dehydroamino acid as is shown in Scheme II, Method 4 (see Asymmetric Synthesis, Vol. 5, (Morrison, ed.) Academic Press, New York, 1985). A comprehensive treatise on the preparation of b-amino acid derivatives may be found in patent application WO 9307867, the disclosure of which is hereby incorporated by reference.

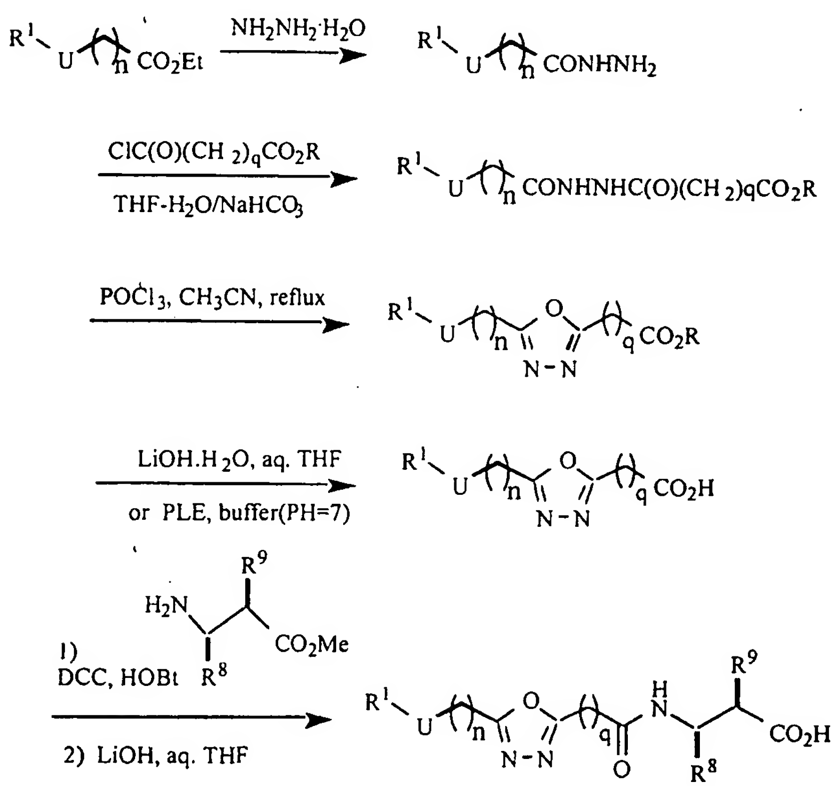
Scheme II



The synthesis of N^2-substituted diaminopropionic acid derivatives can be carried out via Hoffman rearrangement of a wide variety of asparagine derivatives as described in Synthesis, 266-267, (1981).

Synthesis of compounds of Formula I wherein the central heterocycle is a 1,3,4-oxadiazole ring, e.g. G=O, is shown in Scheme III. Cyclization of an appropriately substituted N,N'-diacylhydrazine in the presence of $POCl_3$ according to the method of Klingsberg (J. Am. Chem. Soc. 1958, **80**, 5788) gives the intermediate 1,3,4-oxadiazolyl ester. This ester can be converted to compounds of Formula I using the methods described herein.

Scheme III

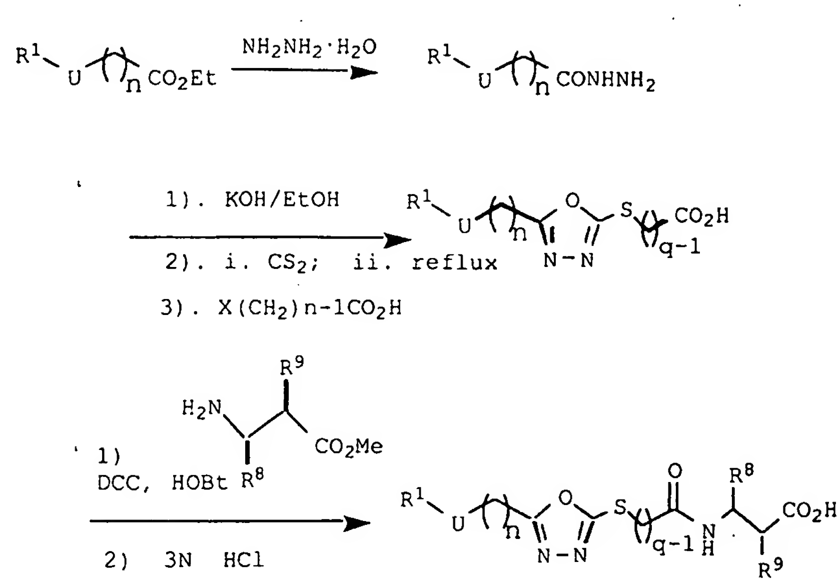


Alternately, the 1,3,4-oxadiazoles may be prepared from an ester bearing an appropriate functional group

such as nitro or vinyl group which can be converted into R^1 at an appropriate stage of the synthesis of the target molecules.

Componds of formula I wherein G=O and W is -$SCH_2C(=O)N(R^{10})$- may be prepared from an appropriately substituted acylhydrazine adopting the method described by Confalone(J. Am. Che. Soc. 1983, **105**, 902), as depicted in Scheme IV.

Scheme IV.



The detailed processes for preparing the compounds of Formula I are illustrated by the following Examples. It is, however, understood that this invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) were measured in chloroform-d ($CDCl_3$) unless otherwise specified and the peaks are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). The coupling patterns are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; m, multiplet.

Example 43

2(S)-Phenylsulfonylamino-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acetyl]aminopropionic acid

Part A. 4-nitrobutyrylhydrazine

Methyl 4-nitrobutyrate(5.5g, 37.5mmol) and hydrazine monohydrate(1.88g, 37.5mmol) were mixed in methanol(30ml). The resulting solution was stirred at rt for 50hrs, and then evaporated under reduced pressure. The oily residue was pure enough for next reaction. ^{1}H NMR(300MHz)δ2.08(qt, 2H), 2.20(t, 2H), 4.50(t, 2H); MS(HH$_3$-CI) Calc. for $(M+1)^+$:148. Found: 148.

Part B.N-(4-Nitrobutyryl)-N' (methoxycarbonylacetyl)hydrazine

To a suspesion of 4-nitrobutyrylhydrazine(5.5g, 37.5mmol) in aqueous THF(80ml, 1:1 v/v) containing sodium bicarbonate(4.1g, 48.8mmol), cooled with ice-water, was added methyl malonyl chloride(6.1g, 44.8mmol) dropwise. After addition, the ice-water bath was removed and the mixture was stirred at rt for 2hrs. The THF was evaporated under reduced pressure and the product as a solid powder was then collected by filtration and dried.(7.9g, 85% yield). ^{1}H NMR(300MHz) δ2.10(qt, 2H), 2.25(t, 2H), 3.34(s, 2H), 3.62(s,3H), 4.79(t, 2H), 10.02(s, 1H), 10.10(s, 1H); MS(NH$_3$-DCI) Calc. for$(M+NH_4)^+$: 265. Found: 265.

Part C. Methyl 2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acetate

A mixture of N-(4-nitrobutyryl)-N'-(methoxycarbonylacetyl)hydrazine(2.0g, 8.1mmol) and Lawesson's reagent(1.8g, 4.4mmol) in anhydrous THF(30ml) was gently refluxed for 1hr. The solution was then evaporated to dryness and the residue was dissolved in ethyl acetate and washed with saturated $NaHCO_3$, brine, then dried. Evaporation followed by chromatography using a mixture of ethyl acetate and hexane (1:1. v:v) as eluent gave the product as an oil(1.1g, 56% yield). ^1H NMR(300MHz) δ2.60(qt, 2H), 3.24(t, 2H), 3.80(s, 3H), 4.10(s, 2H), 4.60(t, 2H) ; MS(NH_3-CI) Calc. for $(M+1)^+$: 246. Found: 246.

Part D. 2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acetic acid

Methyl 2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acetate(1.05g, 4.3mmol) was dissolved in aqueous THF(30ml, 1:1, v:v) containing 450mg(10.7mmol) of $LiOH.H_2O$. The solution was stirred at rt for 8hrs, and then acidified with 6N HCl to a PH of around 2.0. The solution was evaporated to dryness and the residue was washed with acetone. After removal of acetone, the product was dried(800mg, 81% yield). ^1H NMR(300MHz, DMSO) δ2.34(qt, 2H), 3.16(t, 2H), 4.18(s, 2H), 4.68(t, 2H); MS(NH_3-CI) Calc. for $(M+1)^+$: 232. Found: 232.

Part E. Methyl N^2-Cbz-*L*-2,3-diaminopropionate HCl salt.

N^2-Cbz-*L*-2,3-diaminopropionic acid (10 mmol, 2.39 g) was dissolved in 20 mL methanol and 20 mL 4 N HCl in dioxane and the solution was stirred for 4 hours and then concentrated to give a solid. The solid was washed with ether several times to give 2.50 g (87%) product. NMR (DMSO-d_6): d 8.38 (b, 3H); 7.96 (d, 1H); 7.38 (m,

5H); 5.05 (s, 2H); 4.44 (m, 1H); 3.66 (s, 3H); 3.14 (m, 2H).

Part F: Methyl N^2-Cbz-N^3-Boc-*L*-2,3-diaminopropionate.

To a solution of methyl N^2-Cbz-(S)-2,3-diaminopropionate HCl salt (16.3 mmol, 4.7 g) and di-tert-butyl dicarbonate (16.3 mmol, 3.56 g) in 30 mL chloroform cooled in an ice bath was added triethylamine (34 mmol, 4.7 mL) and the solution was stirred in the ice bath for 1 hour and at room temperature for 3 hours and concentrated. The residue was taken up in ethyl acetate and the solution was washed with dilute citric acid, brine, $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Crystallization from ether/petroleum ether gave 5.2 g (92%) product. NMR (DMSO-d_6): d 7.60 (d, 1H); 7.35 (m, 5H); 6.88 (t, 1H); 5.02 (s, 2H); 4.14 (m, 1H); 3.60 (s, 3H); 3.28 (m, 2H); 1.37 (s, 9H).

Part G: Methyl N^3-Boc-(S)-2,3-diaminopropionate Formic acid salt.

A mixture of methyl N^2-Cbz-N^3-Boc-(S)-2,3-diaminopropionate. (14 mmo, 5.0 g), formic acid (42 mmol, 1.6 mL) and 10% Pd/C (500 mg) in 40 mL methanol was stirred at room temperature for 1 hour and filtered through a celite. The filtrate was concentrated and the residue was triturated with ether-petroleum ether to give 3.7 g (100%) solid product. NMR (DMSO-d_6): δ 8.20 (s, 1H); 6.90 (t, 1H); 5.36 (b, 3H); 3.61 9s, 3H); 3.51 (t, 1H); 3.18 (t, 2H); 1.38 (s, 9H).

Part H. Methyl N^2-phenylsulfonyl-N^3-Boc-(S)-2,3-diaminopropionate.

To a mixture of methyl N^3-Boc-(S)-2,3-diaminopropionate HCO_2H salt (3.8g, 14.7mmol) and diisoproppylethylamine(3.3g, 32.3mmol) in CH_2Cl_2(60ml), cooled with ice-water, was added phenylsulfonyl chloride(2.86g, 16.2mmol). After stirring at rt for 24hrs, the resulting reaction mixture was diluted with ethyl acetate(150ml), washed with dilute citric acid, saturated $NaHCO_3$ and brine, and then dried. Concentration afforded the product as a foam(5.0g, 95% yield). ^1H NMR(300MHz)δ1.52(s, 9H), 3.46(m, 2H), 3.56(s, 3H), 4.00(m, 1H), 5.00(m, 1H), 5.74(d, 1H), 7.56(m, 3H), 7.82(m, 2H); MS(NH_3-CI) Calc. for $(M+1)^+$: 359. Found: 359.

Part I. <u>Methyl N^2-phenylsulfonyl-(S)-2,3-diaminopropionate HCl salt</u>

Methyl N^2-phenylsulfonyl-N^3-Boc-(S)-2,3-diaminopropionate(4.5g, 12.6mmol) was dissolved in dioxane(8ml) and then 4N HCl in dioxane(8ml) was added. The resulting solution was stirred at rt for 5hrs and then evaporated to give a foam(3.7g, 100% yield). ^1H NMR(300MHz, DMSO-d_6)δ2.78(m, 2H), 3.56(s, 3H), 3.68(m, 1H), 5.70(d, 1H), 7.46(m, 3H), 7.68(m, 2H); MS(ESI) Calc. for $(M+1)^+$: 259. Found: 259(free base).

Part J. <u>Methyl 2(S)-phenylsulfonyl-3-[2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acety]diaminopropionate.</u>

To a mixture of 2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acetic acid(510mg, 2.2mmol), methyl N^2-phenylsulfonyl-(S)-2,3-diaminopropionate HCl salt(650mg, 2.2mmol) and triethylamine(1.35ml, 8.8mmol) in DMF(12ml), cooled with ice-water, was added TBTU(700g, 2.2mmol). After stirring for 3hrs, the

reaction mixture was diluted with ethyl acetate and washed with dilute citric acid, dilute $NaHCO_3$ and brine successively, then dried. Concentration followed by chromatography using a mixture of ethyl acetate and hexane as the eluent gave the product as an amorphous solid(645mg, 62% yield). ^1H NMR(300MHz)δ2.58(qt, 2H), 3.26(t, 2H), 3.54(m, 1H), 3.58(s, 3H), 3.70(m, 1H), 4.02(m, 1H), 4.08(s, 2H), 4.58(t, 2H), 5.76(d, 1H), 7.08(s, 1H), 7.54(m, 3H), 7.80(m, 2H); MS(NH_3-CI) Calc. for $(M+1)^+$: 472. Found: 472.

Part K. Methyl 2(S)-phenylsulfonyl-3-[2-[2-(3-aminopropyl)-1,3,4-thiadiazol-5 yl]acety]diaminopropionate AcOH salt.

Methyl 2(S)-phenylsulfonyl-3-[2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acetyl]diaminopropionate(400mg, 0.85mmol) was dissolved in a mixed solvent of methanol and acetic acid(12ml, 1:1, v:v) and PtO_2(40mg) was added. The resulting mixture was hydrogenated in a shaking bottle for 30hrs, and then was filtered through a short column of Zeliot. The filtrate was concentrated and the residue dried to give an oily product(410mg, 96% yield). ^1H NMR(300MHz, DMSO-d_6)δ2.76(qt, 2H), 3.08(t, 2H), 3.20(t, 2H), 3.34(s, 3H), 3.38(m, 2H), 3.90(m, 3H), 7.58(m, 3H), 7.749m, 2H), 8.749s, 1H); MS(NH_3-CI) Calc. for $(M+1)^+$: 442. Found: 442.

Part L. Methyl 2(S)-phenylsulfonyl-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5 -yl]acety]diaminopropionate.

A solution of methyl 2(S)-phenylsulfonyl-3-[2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acetyl]diaminopropionate(425mg, 0.85mmol) and 2-methylthio-2-imidazoline hydriode(207mg, 0.85mmol) in

pyridine(10ml) was heated at 70°C for 5hrs. The solution was then concentrated and the residue was chromatographed using a mixture of methylene chloride and methanol as the eluent to afford an oily pruduct(250mg, 58% yield). ^{1}H NMR(300MHz, CD_3OD)δ2.08(qt, 2H), 3.18(t, 2H), 3.30(m, 3H), 3.40(s, 3H), 3.54(dd, 1H), 3.66(s, 4H), 4.00(s, 2H), 4.10(dd, 1H), 7.52(m, 3H), 7.80(m, 2H); MS(ESI) Calc. for $(M+1)^+$: 510. Found: 510.

Part M. 2(S)-phenylsulfonyl-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acety]diaminopropionic acid HCl salt.

Methyl 2(S)-phenylsulfonyl-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5 -yl]acety]diaminopropionate(230mg, 0.45mmol) was dissolved in 4N HCl(9ml) and the solution was stirred at rt for 40hrs, then concentrated under reduced pressure to dryness to afford the product as an amorphous solid(200mg, 91% yield). Further puriofication via reverse phase HPLC using a mixture of acetonitrile and 0.1% TFA in water as the eluent gave the test sample. ^{1}H NMR(300MHz, DMSO-D_6)δ1.96(qt, 2H), 3.08(t, 2H), 3.24(m, 3H), 3.40(m, 1H), 3.90(m, 3H), 7.56(m, 3H), 7.58(m, 2H), 8.22(d, 1H), 8.46(t, 1H), 8.56(t, 1H); MS(ESI) Calc. for $(M+1)^+$: 496. Found: 496.

Example 44

2(S)-(3-methylphenylsulfonyl)amino-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acetyl]aminopropionic acid

Part A. Methyl N^2-3-methylphenylsulfonyl-N^3-Boc-(S)-2,3-diaminopropionate.

To a mixture of methyl N^3-Boc-(S)-2,3-diaminopropionate HCO_2H salt (3.8g, 14.7mmol) and diisoproppylethylamine(3.3g, 32.3mmol) in CH_2Cl_2(60ml), cooled with ice-water, was added 3-methylsulfonyl chloride(3.1g, 16.2mmol). After stirring at rt for 24hrs, the resulting reaction mixture was diluted with ethyl acetate(150ml), washed with dilute citric acid, saturated $NaHCO_3$ and brine, and then dried. Concentration afforded the product as a foam(5.1g, 95% yield). ^1H NMR(300MHz, $CDCl_3$)δ1.58(s, 9H), 2.30(s, 3H), 2.72(m, 1H), 2.98(m, 1H), 4.10(m, 1H), 5,80(s, 1H), 7.40(d, J=5, 2H), 7.50(m, 1H), 7.56(s, 1H), 8.40(d, J=6, 1H); MS(NH_3-CI) Calc. for $(M+1)^+$: 373. Found: 373.

Part B. Methyl N^2-3-methylphenylsulfonyl-(S)-2,3-diaminopropionate HCl salt

Methyl N^2-3-methylphenylsulfonyl-N^3-Boc-(S)-2,3-diaminopropionate(4.5g, 12.1mmol) was dissolved in dioxane(8ml) and then 4N HCl in dioxane(8ml) was added. The resulting solution was stirred at rt for 5hrs and then evaporated to give a foam(3.7g, 100% yield). ^1H NMR(300MHz, DMSO-d_6)δ2.40(s, 3H), 2.86(m, 1H), 3.10(m, 1H), 3.40(s, 3H), 4.28(m, 1H), 7.48(d,J=5 2H), 7.60(m, 1H), 7.62(s, 1H) 8.39(s, broad, 2H), 8.62(d, J=6, 1H); MS(ESI) Calc. for $(M+1)^+$: 273. Found: 273(free base).

Part C. Methyl 2(S)-(3-methylphenyl)sulfonylamino-3-[2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acety]aminopropionate.

To a mixture of 2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acetic acid(430mg, 1.86mmol), methyl N^2-3-methylphenylsulfonyl-(S)-2,3-diaminopropionate HCl salt(630mg, 2.0mmol) and triethylamine(1.1ml, 8.2mmol) in DMF(10ml), cooled with ice-water, was added

TBTU(660mg, 2.0mmol). After stirring for 3hrs, the reaction mixture was diluted with ethyl acetate and washed with dilute citric acid, dilute $NaHCO_3$ and brine successively, then dried. Concentration followed by chromatography using a mixture of ethyl acetate and hexane as the eluent gave the product as an amorphous solid(360mg, 40% yield). ^1H NMR(300MHz)δ2.40(s, 3H), 2.58(qt, 2H), 3.269t, 2H), 3.52(s, 3H), 3.62(m, 2H), 4.06(m, 1H), 4.10(s, 2H), 4.59(t, 2H), 7.36(m, 2H), 7.60(m, 2H); MS(NH_3-CI) Calc. for $(M+1)^+$: 486. Found: 486.

Part D. <u>Methyl 2(S)-(3-methylphenyl)sulfonylamino-3-[2-[2-(3-aminopropyl)-1,3,4-thiadiazol-5-yl]acety]aminopropionate AcOH salt.</u>

Methyl 2(S)-(3-methylphenyl)sulfonylamino-3-[2-[2-(3-nitropropyl)-1,3,4-thiadiazol-5-yl]acetyl]aminopropionate(140mg, 0.29mmol) was dissolved in a mixed solvent of methanol and acetic acid(20ml, 1:1, v:v) and PtO_2(30mg) was added. The resulting mixture was hydrogenated in a shaking bottle for 24hrs, and then was filtered through a short column of Zeliot. The filtrate was concentrated and the residue dried to give an oily product(120mg, 91% yield). ^1H NMR(300MHz, DMSO-d_6)δ1.90(qt, 3H), 2.56(s, 3H), 2.78(t, 2H), 3.10(t, 2H), 3.28(s, 3H), 3.36(m, 2H), 3.84(m, 3H), 7.30(m, 2H), 7.42(m, 1H), 7.74(d, 1H), 8.58(s, 1H); MS(ESI) Calc. for $(M+1)^+$: 456. Found: 456.

Part E. <u>Methyl 2(S)-(3-methylphenyl)sulfonylamino-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acety]aminopropionate.</u>

A solution of methyl 2(S)-(3-methylphenyl)sulfonylamino-3-[2-[2-(3-nitropropyl)-

1,3,4-thiodiazol-5-yl]acetyl]aminopropionate(130mg, 0.29mmol) and 2-methylthio-2-imidazoline hydriode(78mg, 0.32mmol) in pyridine(5ml) was heated at 70°C for 5hrs. The solution was then concentrated and the residue was chromatographed using a mixture of methylene chloride and methanol as the eluent to afford an oily pruduct(90mg, 59% yield). ^1H NMR(300HMz, DMSO-d_6)δ1.90(qt, 3H), 2.56(s, 3H), 3.04(t, 2H), 3.20(m, 2H), 3.28(s, 3H), 3.58(m, 2H), 3.56(m, 4H), 3.84(m, 3H), 7.30(m, 2H), 7.42(m, 1H), 7.74(d, 1H), 8.24(s, 1H), 8.46(s, 1H); MS(ESI) Calc. for $(M+1)^+$: 524. Found: 524.

Part F. <u>2(S)-(3-methylphenyl)sulfonylamino-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acety]aminopropionic acid HCl salt.</u>

Methyl 2(S)-(3-methylphenyl)sulfonylamino-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acety]aminopropionate(80mg, 0.15mmol) was dissolved in 4N HCl(6ml) and the solution was stirred at rt for 36hrs, then concentrated under reduced pressure to dryness, affording the product as an amorphous solid(75mg, 97% yield). Further puriofication via reverse phase HPLC using a mixture of acetonitrile and 0.1% TFA in water as the eluent gave the test sample. ^1H NMR(300MHz, DMSO-D_6)δ2.96(qt, 2H), 2.60(s, 3H), 3.08(t, 2H), 3.20(m, 3H), 3.40(m, 1H), 3.58(s, 4H), 3.94(m, 3H), 7.30(m, 3H), 7.42(m, 1H), 7.58(m, 2H), 8.20(d, 1H), 8.38(t, 1H), 8.50(m, 1H); MS(ESI) Calc. for $(M+1)^+$: 510. Found: 510.

<u>Example 176</u>

<u>2(S)-Benzyloxycarbonylamino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt</u>

Part A. Pent-4-enoyl hydrazide

A mixture of pent-4-enoic acid ethyl ester(12.1g, 94.5mmol) and hydrazine monohydrate(4.6ml, 94.5mmol) in methanol(75ml) was stirred at rt for 48hrs. The volatile portion of the reaction mixture was then removed. The product was obtained as an oil(9.5g, 94% yield). ^{1}H NMR(300MHz)δ1.56(m, 2H), 2.30(t, 2H), 5.20(m, 2H), 5.80(m, 1H); MS(NH_3-CI) Calcd. for $(M+1)^+$: 115. Found: 115.

Part B. N-(Pent-4-enoic)-N'-(methoxycarbonylcarbonyl)hydrazine

To a solution of pent-4-enoic hydrazine(10.8g, 94.5mmol) in aqueous THF(80ml, 1:1, v:v) containing $NaHCO_3$(11.9g, 141.7mmol) cooled in an ice-water bath was added methyl oxalyl chloride(13.0ml, 141.7mmol) dropwise. After addition, the mixture was stirred in the ice-water bath for additional 30mins, and then at rt overnight. The THF was removed under reduced pressure, and the aqueous residue was extracted with ethyl acetate. The ethyl acetate solution was washed with brine and then dried over Na_2SO_4. Concentration afforded the product as an oil(12.3g, 65% yield). ^{1}H NMR(300MHz)δ1.60(qt, 2H), 2.44(t, 2H), 3.96(s, 3H), 5.10(m, 2H), 5.80(m, 1H); MS(NH_3-CI) Calcd. for $(M+1)^+$: 201. Found: 201.

Part C. Methyl [2-(but-3-enyl)-1,3,4-thiadiazol-5-yl]carboxylate

N-(Pent-4-enoic)-N'-(methoxycarbonylcarbonyl)hydrazine(2.13g, 10.6mmol) was dissolved in anhydrous THF(20ml) and then was heated to gentle refluxing. Lawesson reagent(2.15g, 5.3mmol) was

introduced and stirring was continued under such conditions for 3hrs. The solvent was removed under reduced pressure and the residue was dissloved in ethyl acetate, washed with saturated $NaHCO_3$ and brine, then dried over Na_2SO_4. After removal of ethyl acetate, the residue was chromatographed using a mixture of ethyl acetate and hexane as the eluent to give the product as a white solid(1.5g, 73% yield). ^1H NMR(300MHz)δ2.60(qt, 2H), 3.32(t, 2H), 4.06(s, 3H), 5.14(m, 2H), 5.84(m, 1H); MS(NH_3-CI) Calcd. for $(M+1)^+$: 199. Found: 199.

Part C. <u>Methyl [2-(4-hydroxybutyl)-1,3,4-thiadiazol-5-yl]carboxylate</u>

Methyl [2-(but-3-enyl)-1,3,4-thiadiazol-5-yl]carboxylate(420mg, 2.13mmol) was dissolved in anhydrous THF(5ml) and then cooled with an ice-water bath to 0°C. 9-BBN(290mg, 2.34mmol) dissolved in THF(5ml) was introduced and the resulting reaction mixture was kept stirring at 0°C for 3hrs, then at rt for 5hrs. NaOAc(1g) dissolved in water(5ml) was added, followed by introduction of 1ml of 30% H_2O_2. After stirred further at rt for 2hrs, the mixture was extracted with ethyl acetate. The extract was washed with brine and then dried over Na_2SO_4. Concentration followed by chromatography using ethyl acetate as the eluent yielded the product as a white powder(420mg, 92% yield). ^1H NMR(300MHz)δ1.64(m, 2H), 1.90(m, 2H), 3.24(t, 2H), 3.76(q, 2H), 3.82(t, 1H), 4.06(s, 1H); MS(NH_3-CI) Calcd. for $(M+1)^+$: 217. Found: 217.

Part D. <u>Methyl [2-(4-oxobutyl)-1,3,4-thiadiazol-5-yl]carboxylate</u>

Methyl [2-[4-hydroxybutyl)-1,3,4-thiadiazol-5-yl]carboxylate(210mg, 0.97mmol) was dissloved in

CH_2Cl_2, followed by introduction of PCC(314mg, 1.45mmol). The mixture was stirred at rt for 5hrs, and then was filtered through a short column of silica gel. The filtrate was concentrated and the residue was chromatographed using a mixture of ethyl acetate and hexane as the eluent to give 110mg of the product(53% yield) as a white solid. ^1H NMR(300MHz)δ2.20(qt, 2H), 2.66(t, 2H), 3.26(t, 2H), 4.04(s, 3H), 9.72(s, 1H); MS(NH_3-CI) Calcd. for $(M+1)^+$: 215. Found: 215.

Part E. Methyl [2-[4-[N-Boc-N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carboxylate

Methyl [2-(4-oxobutyl)-1,3,4-thiadiazol-5-yl]carboxylate(100mg, 0.47mmol) and 2-aminopyridine(48mg, 0.52mmol) were dissolved in anhydrous toluene(4ml) and then were heated at 70°C for 2hrs, during which time a small amount of pulverised molecular sieve was added. HOAc(30ul, 0.52mmol) and $NaB(OAc)_3H$ were added. Stirring was continued at rt for 18hrs. NaOAc(300mg) dissolved in 10ml of water was added and the mixture was diluted with another 10ml of water after being stirred for additional 2hrs. The solution was extracted with CH_2Cl_2 and the extract was concentrated and dried.

The oily product obtained above was then dissolved in dry $CHCl_3$(5ml), and cooled in an ice-water bath, followed by addition of triethylamine(0.13ml, 0.94mmol), Boc_2O(153mg, 0.71mmol) and a catalytic amount of DMAP. The mixture was stirred at rt for 24hrs, and then diluted with ethyl acetate. The solution was washed with dilute citric acid, saturated $NaHCO_3$ and brine successively, and then dried over Na_2SO_4. Concetration followed by chromatography using a mixture of ethyl acetate and hexane as the eluent afforded the product as an oil(85mg, 46% yield in two steps). ^1H NMR(300MHz)δ1.50(s, 9H), 1.79(qt,

2H), 1.84(qt, 2H), 3.20(t, 2H), 4.00(t, 2H), 4.04(s, 3H), 7.00(m, 1H), 7.60(m, 2H), 8.38(m, 1H); MS(NH_3-CI) Calcd. for $(M+1)^+$: 393. Found: 393.

Part E. [2-[4-[N-Boc-N-(pyridin-2-yl)amino]butyl] -1,3,4-thiadiazol-5-yl]carboxylic acid

Methyl [2-[4-[N-Boc-N-(pyridin-2-yl)amino]butyl] -1,3,4-thiadiazol-5-yl]carboxylate(80mg, 0.20mmol) dissolved in 0.2ml of DMSO was mixed with PLE(50mg) and buffer solution (PH=7.00, 4ml) and the mixture was vigorously stirred at rt for 18hrs, and then was evaporated under high vaccum. The resulting solid was extracted with ethyl acetate and the extract was concentrated to give an oil(60mg, 78% yield). ^{1}H NMR(300MHz)δ1.52(s, 9H), 1.80(qt, 2H), 1.86(qt, 2H), 3.22(t, 2H), 4.00(t, 2H), 7.10(m, 1H), 7.64(m, 2H), 8.30(m, 1H); MS(ESI) Calcd. for $(M+1)^+$: 379. Found: 379.

Part F. t-butyl 2(S)-benzyloxycarbonylamino-3-aminopropionate

Conc. H2SO4(8ml) was added to dioxane(120ml) in a Parr Bottle cooled with dry ice, followed by addition of 2(S)-benzyloxycarbonylamino-3-aminopropionic acid(6.88g, 28.8mmol) and pre-condensed isobutylene(130ml, excess). The mixture in the Parr bottlle was then shaked at rt for 70hrs. After removal of isobutylene under reduced pressure, the resulting solution was poured into a NaOH solution containing NaOH(17.4g) and ether(400ml) cooled in an ice water bath while stirred vigorously. The etheral layer was separated and the aqueous layer was extracted with ether. The combined etheral solution was washed with 1N HaOH twice and then dried over Na2SO4. Concetration gave the product as a solid(6.3g, 75% yield). ^{1}H

NMR(300MHz)δ1.44(s, 9H), 3.10(m,2H), 4.26(m, 1H), 5.12(s, 2H), 5.80(d, 1H), 7.36(m, 5H); MS(NH_3-CI) Calcd. for $(M+1)^+$: 293. Found: 293.

Part G. t-Butyl 2(S)-Benzyloxycarbonylamino-3-[[2-[4-[N-Boc-N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionate

To a mixture of [2-[4-[N-Boc-N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carboxylic acid (50mg, 0.13mmol), t-butyl 2(S)-benzyloxycarbonylamino-3-aminopropionate(40mg, 0,13mmol) and triethylamine(40ul, 0.29mmol) in EtOAc(4ml), was added PyBop(75mg, 0.13mmol). After stirring for 4hrs at rt, the reaction mixture was diluted with ethyl acetate and washed with dilute citric acid, dilute $NaHCO_3$ and brine successively, then dried. Concentration followed by chromatography using a mixture of ethyl acetate and hexane as the eluent gave the product as an amorphous solid(30mg, 35% yield).^{1}H NMR(300MHz)δ1.46(s, 9H), 1.50(s, 9H), 1.80(m, 4H), 3.19(t, 2H), 3.87(m, 2H), 4.00(t, 2H), 4.44(m, 1H), 5.12(s, 2H), 5.68(d, 1H), 7.00(m, 1H), 7.36(m, 5H), 7.60(m, 2H), 8.40(m, 1H); MS(ESI) Calc. for $(M+1)^+$: 655. Found: 655.

Part H. 2(S)-Benzyloxycarbonylamino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

t-Butyl 2(S)-Benzyloxycarbonylamino-3-[[2-[4-[N-Boc- N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5- yl]carbonyl]aminopropionate(30mg, 0.046mmol) was dissolved in CH_2Cl_2(5ml) containing 0.25ml of TFA. The solution was stirred at rt for 24hrs and then concetrated, affording an oily product(20mg,

87% yield). Further purification by reverse HPLC using a mixture of acetonitrile and 0.1% TFA in water gave the sample for testing. ^{1}H NMR(300MHz)δ1.68(qt, 2H), 1.84(qt, 2H), 3.20(t, 2H), 3.36(m, 2H), 3.64(t, 2H), 4.25(m, 1H), 5.02(s, 2H), 6.84(t, 1H), 7.04(d, 1H), 7.54(m, 5H), 7.70(m, 1H), 7.90(m, 2H), 8.80(m, 1H), 9.20(t, 1H); MS(ESI) Calc. for $(M+1)^+$: 499. Found: 499.

Example 178

2(S)-(2,4,6-Trimethylphenylsulfonyl)amino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

Part A. 2-N-Mesitylenesufonyl-L-asparigine

L-Asparagine(8.5g, 56.8mmol) was dissolved in water(23ml) containing triethylamine(19.8ml). Thi mixture was then diluted with dioxane(40ml). To the resulting mixture was added slowly 2-mesitylenesulfonyl chloride(14.85g) dissolved in dioxane(50ml), causing a little exothermic. After addition, the mixure was stirred further at rt for 24hrs. The reaction mixture was evaporated to remove most of the organic solvent, and then basified with 2N HaOH. The basic solution was extracted with CH2Cl2(50mlX2) and filtered. The filtrate was acidified with concentrated HCl. The solid formed was collected by filtration(13.0g, 73%yield). ^{1}H NMR(300MHz,$CDCl_3$)δ2.24(s, 3H), 2.30(dd, 1H), 2.43(dd, 1H), 2.54(s, 6H), 4.00(m, 1H), 6.86(s, 1H), 7.00(s, 2H), 7.32(s, 1H), 7.80(d, 1H); MS(ESI) Calc. for $(M+1)^+$: 315. Found: 315.

Part B. 2(S)-(2,4,6-Trimethylphenylsulfonyl)amino-3-aminopropionic acid

Bromine(1.04ml, 20.1ml) was added to a solution of 4N NaOH(34ml) cooled in an ice-water bath. The orange solution was stirred in the ice bath for additional 15mins and then 2-N-Mesitylenesufonyl-L-asparigine(5.3g, 16.8mmol) was added in portions. Stirring was continued in the ice bath for 15 mins and then at 85°C for 1 hr. The resulting solution was cooled in an ice bath and acidified with conc. HCl to PH ~6. The solid was collected through filtration(4,7g, 97% yield). ^{1}H NMR(300MHz, DMSO-d_6)δ2.20(s, 3H), 2.48(s, 6H), 2.76(t, 1H), 2.92(m, 1H), 3.04(m, 1H), 6.98(s, 1H), 7.00(s, 2H); MS(ESI) Calc. for $(M+1)^+$: 287. Found: 287.

Part C. <u>t-Butyl 2(S)-(2,4,6 trimethylphenylsulfonyl) amino-3-aminopropionate</u>

Conc. H2SO4(7.7ml) was added to dioxane(120ml) in a Parr Bottle cooled with dry ice, followed by addition of 2(S)-(2,4,6-trimethylphenylsulfonyl)amino-3-aminopropionic acid(8,02g, 28mmol) and pre-condensed isobutylene(136ml, excess). The mixture in the Parr bottlle was then shaked at rt for 70hrs. After removal of isobutylene under reduced pressure, the resulting solution was poured into a NaOH solution containing NaOH(11.9g) and ether(400ml) cooled in an ice water bath while stirred vigorously. The etheral layer was separated and the aqueous layer was extracted with ether. The combined etheral solution was washed with 1N HaOH twice and then dried over Na2SO4. Concetration gave the product as a solid(7.7g, 81% yield). ^{1}H NMR(300MHz)δ1.56(s, 9H), 2.20(s, 3H), 2.48(s, 6H), 2.76(t, 1H), 2.92(m, 1H), 3.04(m, 1H), 6.98(s, 1H), 7.00(s, 2H) ; MS(NH_3-CI) Calcd. for $(M+1)^+$: 343. Found: 343.

Part D. t-Butyl 2(S)-(2,4,6-trimethylphenylsulfonyl) amino-3-[2-[4-[N-Boc-N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionate

To a mixture of [2-[4-[N-Boc-N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carboxylic acid (135mg, 0.36mmol), t-butyl 2(S)-(2,4,6-trimethylphenylsulfonyl)amino-3-aminopropionate(120mg, 0.36mmol) and triethylamine(0.25 ml, 1.8 mmol) in DMF(8 ml), was added PyBop(210 mg, 0.36 mmol). After stirring for 4 hrs at rt, the reaction mixture was diluted with ethyl acetate and washed with dilute citric acid, dilute $NaHCO_3$ and brine successively, then dried. Concentration followed by chromatography using a mixture of ethyl acetate and hexane as the eluent gave the product as an amorphous solid(150 mg, 64% yield). ^1H NMR(300MHz, $CDCl_3$)δ1.32(s, 9H), 1.50(s, 9H), 1.82(m, 4H), 2.24(s, 3H), 2.64(s, 6H), 3.20(t, 2H), 3.66(m, 1H), 3.80(m, 1H), 4.00(m, 3H), 5.60(d, 1H), 6.90(s, 2H), 7.00(m, 1H), 7.60(m, 2H), 8.40(m, 1H); MS(ESI) Calc. for $(M+1)^+$: 703. Found: 703.

Part E. 2(S)-(2,4,6-Trimethylphenylsulfonyl)amino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

t-Butyl 2(S)-(2,4,6 trimethylphenylsulfonyl) amino-3-[[2-[4-[N-Boc-N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionate(60mg, 0.091mmol) was dissolved in CH_2Cl_2(5ml) containing 0.25ml of TFA. The solution was stirred at rt for 24hrs and then concetrated, affording an oily product(42mg, 90% yield). Further purification by reverse HPLC using a mixture of acetonitrile and 0.1% TFA in water gave the sample for testing. ^1H NMR(300MHz, DMSO-d_6)δ1.64(qt, 2H), 1.80(qt, 2H),2.12(s, 3H), 2.46(s,

6H), 3.18(t, 2H), 3.30(m, 2H), 3.50(m, 2H), 3.98(m, 1H), 6.80(s, 2H), 6.84(t, 1H), 7.00(d, 1H), 7.86(m, 2H), 8.02(d, 1H), 8.76(s, 1H), 8.94(t, 1H); MS(ESI) Calc. for $(M+1)^+$: 547. Found: 547.

Example 179

2(S)-(1-Naphthalenesulfonyl)amino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

This compound was analogously prepared to Example 178. ^1H NMR(300MHz, DMSO-d_6)δ1.64(qt, 2H), 1.80(qt, 2H), 3.18(t, 2H), 3.34(m, 2H), 3.44(m, 2H), 3.90(m, 1H), 6.80(t, 1H), 7.00(d, 1H), 7.50(m, 3H), 7.88(m, 3H), 8.06(d, d, 2H), 8.56(d, 2H), 8.76(s, 1H), 8.84(t, 1H); MS(ESI) Calc. for $(M+1)^+$: 555. Found: 555.

Example 321

2(S)-Benzyloxycarbonylamino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

Part A. Methyl [2-(4-triazobutyl)-1,3,4-thiadiazol-5-yl]carboxylate

Mesyl chloride(0.26 mL, 3.34 mmol) was added slowly to a solution of methyl [2-(4-hydroxybutyl)-1,3,4-thiadiazol-5-yl]carboxylate(600 mg, 2.78 mmol) and triethylamine(0.77ml, 5.56 mmol) in CH_2Cl_2 cooled in a ice-water bath. After addition, the resulting mixture was stirred for additional 30 mins. The reaction mixture was diluted with ethyl acetate and then washed

with aqueous citric acid, saturated NaHCO3 and brine. Concentration and chromatography with a mixture of ethyl acetate and hexane gave the mesylate as an oil(530mg).

The mesylate was dissolved in DMF(10ml). Sodium triazide(585 mg, 9.0 mmol) was added. The mixture was heated at 40 _C for 4 hrs. After dilution with ethyl acetate, the organic solution was washed with saturated $NaHCO_3$, brine and then dried over Na_2SO_4. Concetration and Chromatography with a mixture of ethyl aceate and hexane gave 450 mg of the product as an oil(67% yield). ^1H NMR(300MHz, $CDCl_3$)δ1.74(m, 2H), 1.96(m, 2H), 3.24(t, 2H), 3.38(t, 2H),4.06(s, 1H); MS(NH_3-CI) Calcd. for $(M+1)^+$: 242. Found: 242.

Part B. <u>[2-(4-triazobutyl)-1,3,4-thiadiazol-5-yl]carboxylic acid</u>

Methyl [2-[4-triazobutyl]-1,3,4-thiadiazol-5-yl]carboxylate(300 mg, 1.24 mmol) was mixed with PLE-A(200 mg) and buffer solution(PH=7.00, 10 ml). The mixture was vigorously stirred at rt for 36 hrs, and then evaporated under high vaccum to dryness. The residue was extracted with methanol and the extract was concentrated to give the aciod as an oil(190 mg, 70% yield). ^1H NMR(300MHz, DMSO-d_6)δ1.58(m, 2H), 1.76(m, 2H), 3.00(t, 2H), 3.40(t, 2H); MS(ESI) Calcd. for $(M+1)^+$: 228. Found: 228.

Part C. <u>t-Butyl 2(S)-benzyloxycarbonylamino-3-[[2-(4-triazobutyl)-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionate</u>

To a mixture of [2-(4-triazobutyl)-1,3,4-thiadiazol-5-yl]carboxylic acid(270 mg, 1.2 mmol), t-butyl 2(S)-benzyloxycarbonylamino-3-aminopropionate(350 mg, 0,13mmol) and triethylamine(40ul, 1.2 mmol) in

DMF(10 ml), was added PyBop(700 mg, 1.2 mmol). After stirring for 4hrs at rt, the reaction mixture was diluted with ethyl acetate and washed with dilute citric acid, dilute $NaHCO_3$ and brine successively, then dried. Concentration followed by chromatography using a mixture of ethyl acetate and hexane as the eluent gave the product as an amorphous solid(440 mg, 90% yield). ^1H NMR(300MHz, $CDCl_3$)δ1.40(s, 9H), 1.74(m, 2H), 1.85(m, 2H), 3.20(t, 2H), 3.26(t, 2H), 3.88(m, 2H), 4.10(m, 1H), 5.12(S, 2H), 5.80(s, 1H), 7.38(m, 5H), 7.68(s, 1H); MS(ESI) Calc. for $(M+1)^+$: 604. Found: 604.

Part D. t-Butyl 2(S)-benzyloxycarbonylamino-3-[[2-(4-aminobutyl)-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionate

A solution of t-Butyl 2(S)-benzyloxycarbonylamino-3-[[2-(4-triazobutyl)-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionate (240 mg, 0.48 mmol), triphenylphosphine(125 mg, 0.48 mmol) in THF(10 ml) was heated to reflux for 3 hrs and then stirred at rt overnight. Water(10 mg, 0.55 mmol) was injected and the reaction mixture was stirred at rt for additional 24 hrs. Concentration followed by chromatography with a mixture of CH_2Cl_2, methanol and ammonium hydroxide gave the product as an oil(150 mg, 66% yield). ^1H NMR(300MHz, DMSO-d_6)δ1.28(s, 9H), 1.40(m, 2H), 1.70(m, 2H), 2.54(t, 2H), 3.10(t, 2H), 3.72(m, 1H), 3.84(m, 1H), 4.20(m, 1H), 5.00(s, 2H), 7.30(m, 5H), 7.76(d, 1H); MS(ESI) Calc. for $(M+1)^+$: 478. Found: 478.

Part E. t-Butyl 2(S)-Benzyloxycarbonylamino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionate

A mixture of t-Butyl 2(S)benzyloxycarbonylamino

-3-[[2-(4-triazobutyl)-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionate(100 mg, 0.21 mmol) and 2-imidazolidinethione hydrogen iodide(61 mg, 0.25 mmol) in pyridine(5 mL) was stirred at 70 _C for 3 hrs. Concentration and chromatography with a mixture of CH_2Cl_2 and methanol as the eluent gave the product as an amorphous solid(60 mg, 53% yield). ^1H NMR(300MHz, DMSO-d_6)δ1.28(s, 9H), 1.54(m, 2H), 1.76(m, 2H), 3.10(t, 2H), 3.42(m, 2H), 3.60(m, 2H), 4.20(m, 1H), 5.00(s, 2H), 7.30(m, 5H), 7.78(d, 1H), 8.20(t, 1H), 9.20(t, 1H); MS(ESI) Calc. for $(M+1)^+$: 546. Found: 546.

Part E, 2(S)-Benzyloxycarbonylamino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

t-Butyl 2(S)-benzyloxycarbonylamino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionate(100 mg, 0.18 mmol) was dissolved in CH_2Cl_2 containg 0.25 mL of TFA. The solution was stirred at rt for 24 hrs. Concentration gave the product(80 mg, 89% yield). ^1H NMR(300MHz, DMSO-d_6)δ1.56(m, 2H), 1.86(m, 2H), 3.18(m, 4H), 3.54(m, 1H), 3.58(s, 4H), 3.66(m, 1H), 4.10(m, 1H), 5.00(s, 2H), 7.30(m, 5H), 7.76(d, 1H), 8.16(t, 1H), 9.10(t, 1H); MS(ESI) Calc. for $(M+1)^+$: 491. Found: 491.

Example 327

2(S)-(2,4,6-Trimethylphenylsulfonyl)amino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

This compound was analogously synthesized to Example 321.
^1H NMR(300MHz, DMSO-d_6)1.54(m, 2H), 1.76(m, 2H), 2.20(s, 3H), 2.60(s, 6H), 3.10(m, 4H), 3.42(m, 1H),

3.60(m, 1H), 3.82(s, 4H), 4.20(m, 1H), 6.98(s, 2H), 7.40(d, 2H) 7.78(d, 1H), 8.20(t, 1H), 9.20(t, 1H); MS(ESI) Calc. for $(M+1)^+$: 538. Found: 538.

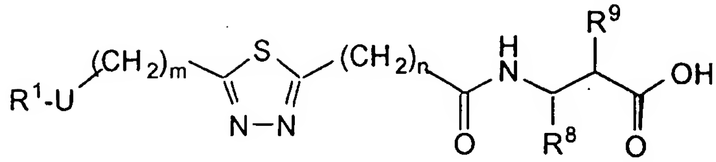
Example 330

2(S)-(1-Naphthalenesulfonyl)amino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

This compound was analogously synthesized to Example 321.

^{1}H NMR(300MHz, DMSO-d_6)δ1.56(m, 2H), 1.74(m, 2H), 3.14(m, 4H), 3.38(m, 1H), 3.48(m, 1H), 3.58(s, 4H), 4.08(m, 1H), 7.60(m, 4H), 7.98(d, 1H), 8.06(d, 1H), 8.16(m, 2H), 8.58(d, 1H), 8.70(d, 1H), 9.12(t, 1H); MS(ESI) Calc. for $(M+1)^+$: 546. Found: 546.

Table 1



Ex. No.	R^1-U	m	n	R^8	R^9	MS
1	tetrahydropyrimidin -2-ylamino	3	1	H	H	
2	tetrahydropyrimidin -2-ylamino	3	1	H	NHCbz	
3	tetrahydropyrimidin -2-ylamino	3	1	H	NHtBOC	
4	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2$-nBu	
5	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2Et$	
6	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2Me$	
7	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO(CH_2)_nPh$	
8	tetrahydropyrimidin -2-ylamino	3	1	H	NHCOtBu	
9	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO-n-C_5H_{11}	
10	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO-n-C_4H_9	
11	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_2CH_3$	
12	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_3$	
13	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2CH_3$	
14	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2CH_2CH_3$	
15	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2$n-Bu	
Ex. No.	R^1-U	m	n	R^8	R^9	MS
16	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2Ph$	
17	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	

18	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2Bn$	
19	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO(2-pyridyl)	
20	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO(3-pyridyl)	
21	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO(4-pyridyl)	
22	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_2$(2-pyridyl)	
23	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_2$(3-pyridyl)	
24	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_2$(4-pyridyl)	
25	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2CH_2$(2-pyridyl)	
26	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2CH_2$(3-pyridyl)	
27	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2CH_2$(4-pyridyl)	
28	imidazolin-2-ylamino	3	1	H	H	
29	imidazolin-2-ylamino	3	1	H	NHCbz	
30	imidazolin-2-ylamino	3	1	H	NHtBOC	
31	imidazolin-2-ylamino	3	1	H	$NHCO_2$-nBu	
32	imidazolin-2-ylamino	3	1	H	$NHCO_2Et$	
33	imidazolin-2-ylamino	3	1	H	$NHCO_2Me$	
34	imidazolin-2-ylamino	3	1	H	$NHCO(CH_2)_nPh$	
35	imidazolin-2-ylamino	3	1	H	NHCOtBu	
Ex. No.	R^1-U	m	n	R^8	R^9	MS
36	imidazolin-2-ylamino	3	1	H	NHCO-n-C_5H_{11}	
37	imidazolin-2-ylamino	3	1	H	NHCO-n-C_4H_9	
38	imidazolin-2-ylamino	3	1	H	$NHCOCH_2CH_3$	
39	imidazolin-2-ylamino	3	1	H	$NHCOCH_3$	
40	imidazolin-2-ylamino	3	1	H	$NHSO_2CH_3$	

41	imidazolin-2-ylamino	3	1	H	$NHSO_2CH_2CH_3$	
42	imidazolin-2-ylamino	3	1	H	$NHSO_2$n-Bu	
43	imidazolin-2-ylamino	3	1	H	$NHSO_2Ph$	496
44	imidazolin-2-ylamino	3	1	H	$NHSO_2C_6H_4(3\text{-}CH_3)$	510
45	imidazolin-2-ylamino	3	1	H	$NHSO_2Bn$	
46	imidazolin-2-ylamino	3	1	H	NHCO(2-pyridyl)	
47	imidazolin-2-ylamino	3	1	H	NHCO(3-pyridyl)	
48	imidazolin-2-ylamino	3	1	H	NHCO(4-pyridyl)	
49	imidazolin-2-ylamino	3	1	H	$NHCOCH_2$(2-pyridyl)	
50	imidazolin-2-ylamino	3	1	H	$NHCOCH_2$(3-pyridyl)	
51	imidazolin-2-ylamino	3	1	H	$NHCOCH_2$(4-pyridyl)	
52	imidazolin-2-ylamino	3	1	H	$NHCO_2CH_2$(2-pyridyl)	
53	imidazolin-2-ylamino	3	1	H	$NHCO_2CH_2$(3-pyridyl)	
54	imidazolin-2-ylamino	3	1	H	$NHCO_2CH_2$(4-pyridyl)	
55	tetrahydropyrimidin-2-ylamino	4	0	H	H	

Ex. No.	R^1-U	m	n	R^8	R^9	MS
56	tetrahydropyrimidin-2-ylamino	4	0	H	NHCbz	
57	tetrahydropyrimidin-2-ylamino	4	0	H	NHtBOC	
58	tetrahydropyrimidin-2-ylamino	4	0	H	$NHCO_2$-nBu	
59	tetrahydropyrimidin-2-ylamino	4	0	H	$NHCO_2Et$	
60	tetrahydropyrimidin-2-ylamino	4	0	H	$NHCO_2Me$	
61	tetrahydropyrimidin-2-ylamino	4	0	H	$NHCO(CH_2)_nPh$	
62	tetrahydropyrimidin-2-ylamino	4	0	H	NHCOtBu	
63	tetrahydropyrimidin-2-ylamino	4	0	H	NHCO-n-C_5H_{11}	

64	tetrahydropyrimidin -2-ylamino	4	0	H	NHCO-n-C_4H_9	
65	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_2CH_3$	
66	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_3$	
67	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2CH_3$	
68	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2CH_2CH_3$	
69	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2$n-Bu	
70	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2Ph$	
71	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	
72	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2Bn$	
73	tetrahydropyrimidin -2-ylamino	4	0	H	NHCO(2-pyridyl)	
74	tetrahydropyrimidin -2-ylamino	4	0	H	NHCO(3-pyridyl)	
75	tetrahydropyrimidin -2-ylamino	4	0	H	NHCO(4-pyridyl)	
Ex. No.	R^1-U	m	n	R^8	R^9	MS
76	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_2$(2-pyridyl)	
77	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_2$(3-pyridyl)	
78	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_2$(4-pyridyl)	
79	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCO_2CH_2$(2-pyridyl)	
80	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCO_2CH_2$(3-pyridyl)	
81	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCO_2CH_2$(4-pyridyl)	
82	imidazolin-2-ylamino	4	0	H	H	
83	imidazolin-2-ylamino	4	0	H	NHCbz	
84	imidazolin-2-ylamino	4	0	H	NHtBOC	
85	imidazolin-2-ylamino	4	0	H	$NHCO_2$-nBu	
86	imidazolin-2-ylamino	4	0	H	$NHCO_2Et$	

Ex. No.	R^1-U	m	n	R^8	R^9	MS
87	imidazolin-2-ylamino	4	0	H	$NHCO_2Me$	
88	imidazolin-2-ylamino	4	0	H	$NHCO(CH_2)_nPh$	
89	imidazolin-2-ylamino	4	0	H	NHCOtBu	
90	imidazolin-2-ylamino	4	0	H	NHCO-n-C_5H_{11}	
91	imidazolin-2-ylamino	4	0	H	NHCO-n-C_4H_9	
92	imidazolin-2-ylamino	4	0	H	$NHCOCH_2CH_3$	
93	imidazolin-2-ylamino	4	0	H	$NHCOCH_3$	
94	imidazolin-2-ylamino	4	0	H	$NHSO_2CH_3$	
95	imidazolin-2-ylamino	4	0	H	$NHSO_2CH_2CH_3$	
96	imidazolin-2-ylamino	4	0	H	$NHSO_2$n-Bu	
97	imidazolin-2-ylamino	4	0	H	$NHSO_2Ph$	
98	imidazolin-2-ylamino	4	0	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	
99	imidazolin-2-ylamino	4	0	H	$NHSO_2Bn$	
100	imidazolin-2-ylamino	4	0	H	NHCO(2-pyridyl)	
101	imidazolin-2-ylamino	4	0	H	NHCO(3-pyridyl)	
102	imidazolin-2-ylamino	4	0	H	NHCO(4-pyridyl)	
103	imidazolin-2-ylamino	4	0	H	$NHCOCH_2$(2-pyridyl)	
104	imidazolin-2-ylamino	4	0	H	$NHCOCH_2$(3-pyridyl)	
105	imidazolin-2-ylamino	4	0	H	$NHCOCH_2$(4-pyridyl)	
106	imidazolin-2-ylamino	4	0	H	$NHCO_2CH_2$(2-pyridyl)	
107	imidazolin-2-ylamino	4	0	H	$NHCO_2CH_2$(3-pyridyl)	
108	imidazolin-2-ylamino	4	0	H	$NHCO_2CH_2$(4-pyridyl)	
109	tetrahydropyrimidin-2-ylamino	3	0	H	H	

Ex. No.	R^1-U	m	n	R^8	R^9	MS
110	tetrahydropyrimidin -2-ylamino	3	0	H	NHCbz	
111	tetrahydropyrimidin -2-ylamino	3	0	H	NHtBOC	
112	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2$-nBu	
113	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2Et$	
114	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2Me$	
115	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO(CH_2)_nPh$	
Ex. No.	R^1-U	m	n	R^8	R^9	MS
116	tetrahydropyrimidin -2-ylamino	3	0	H	NHCOtBu	
117	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO-n-C_5H_{11}	
118	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO-n-C_4H_9	
119	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_2CH_3$	
120	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_3$	
121	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2CH_3$	
122	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2CH_2CH_3$	
123	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2$n-Bu	
124	tetrahydropyrimidin -2-ylamino	3	0		$NHSO_2Ph$	
125	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	
126	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2Bn$	
127	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO(2-pyridyl)	
128	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO(3-pyridyl)	
129	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO(4-pyridyl)	
130	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_2$(2-pyridyl)	
131	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_2$(3-pyridyl)	
132	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_2$(4-pyridyl)	

133	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2CH_2$(2-pyridyl)	
134	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2CH_2$(3-pyridyl)	
135	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2CH_2$(4-pyridyl)	
Ex. No.	R^1-U	m	n	R^8	R^9	MS
136	imidazolin-2-ylamino	3	0	H	H	
137	imidazolin-2-ylamino	3	0	H	NHCbz	
138	imidazolin-2-ylamino	3	0	H	NHtBOC	
139	imidazolin-2-ylamino	3	0	H	$NHCO_2$-nBu	
140	imidazolin-2-ylamino	3	0	H	$NHCO_2Et$	
141	imidazolin-2-ylamino	3	0	H	$NHCO_2Me$	
142	imidazolin-2-ylamino	3	0	H	$NHCO(CH_2)_nPh$	
143	imidazolin-2-ylamino	3	0	H	NHCOtBu	
144	imidazolin-2-ylamino	3	0	H	NHCO-n-C_5H_{11}	
145	imidazolin-2-ylamino	3	0	H	NHCO-n-C_4H_9	
146	imidazolin-2-ylamino	3	0	H	$NHCOCH_2CH_3$	
147	imidazolin-2-ylamino	3	0	H	$NHCOCH_3$	
148	imidazolin-2-ylamino	3	0	H	$NHSO_2CH_3$	
149	imidazolin-2-ylamino	3	0	H	$NHSO_2CH_2CH_3$	
150	imidazolin-2-ylamino	3	0	H	$NHSO_2$n-Bu	
151	imidazolin-2-ylamino	3	0	H	$NHSO_2Ph$	
152	imidazolin-2-ylamino	3	0	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	
153	imidazolin-2-ylamino	3	0	H	$NHSO_2Bn$	
154	imidazolin-2-ylamino	3	0	H	NHCO(2-pyridyl)	
155	imidazolin-2-ylamino	3	0	H	NHCO(3-pyridyl)	

Ex. No.	R^1-U	m	n	R^8	R^9	MS
156	imidazolin-2-ylamino	3	0	H	NHCO(4-pyridyl)	
157	imidazolin-2-ylamino	3	0	H	$NHCOCH_2$(2-pyridyl)	
158	imidazolin-2-ylamino	3	0	H	$NHCOCH_2$(3-pyridyl)	
159	imidazolin-2-ylamino	3	0	H	$NHCOCH_2$(4-pyridyl)	
160	imidazolin-2-ylamino	3	0	H	$NHCO_2CH_2$(2-pyridyl)	
161	imidazolin-2-ylamino	3	0	H	$NHCO_2CH_2$(3-pyridyl)	
162	imidazolin-2-ylamino	3	0	H	$NHCO_2CH_2$(4-pyridyl)	
163	4,1,3-oxadiazin-2-ylamino	4	0	H	NHCbz	
164	4,1,3-oxadiazin-2-ylamino	4	0	H	$NHCO_2$-n-Bu	
165	4,1,3-oxadiazin-2-ylamino	4	0	H	$NHSO_2Ph$	
166	4,1,3-oxadiazin-2-ylamino	4	0	H	$NHSO_2$-n-Bu	
167	4,1,3-oxadiazin-2-ylamino	3	1	H	NHCbz	
168	4,1,3-oxadiazin-2-ylamino	3	1	H	$NHCO_2$-n-Bu	
169	4,1,3-oxadiazin-2-ylamino	3	1	H	$NHSO_2Ph$	
170	4,1,3-oxadiazin-2-ylamino	3	1	H	$NHSO_2$-n-Bu	
172	pyridin-2-ylamino	3	1	H	NHCbz	
173	pyridin-2-ylamino	3	1	H	$NHCO_2$-n-Bu	
174	pyridin-2-ylamino	3	1	H	$NHSO_2Ph$	
175	pyridin-2-ylamino	3	1	H	$NHSO_2$-nBu	
176	pyridin-2-ylamino	4	0	H	NHCbz	499

Ex. No.	R^1-U	m	n	R^8	R^9	MS
177	pyridin-2-ylamino	4	0	H	$NHCO_2$-n-Bu	

178	pyridin-2-ylamino	4	0	H	(2,4,6-trimethylph-enylsulfonyl)amino	547
179	pyridin-2-ylamino	4	0	H	(1-naphthalenesul-fonyl)amino	555
180	pyridin-2-ylamino	3	0	H	NHCbz	
181	pyridin-2-ylamino	3	0	H	$NHCO_2$-n-Bu	
182	pyridin-2-ylamino	3	0	H	$NHSO_2Ph$	
183	pyridin-2-ylamino	3	0	H	$NHSO_2$-nBu	
184	imidazol-2-ylamino	3	1	H	NHCbz	
185	imidazol-2-ylamino	3	1	H	$NHCO_2$-n-Bu	
186	imidazol-2-ylamino	3	1	H	$NHSO_2Ph$	
187	imidazol-2-ylamino	3	1	H	$NHSO_2$-nBu	
188	imidazol-2-ylamino	4	0	H	NHCbz	
189	imidazol-2-ylamino	4	0	H	$NHCO_2$-n-Bu	
190	imidazol-2-ylamino	4	0	H	$NHSO_2Ph$	
191	imidazol-2-ylamino	4	0	H	$NHSO_2$-nBu	
192	imidazol-2-ylamino	3	0	H	NHCbz	
193	imidazol-2-ylamino	3	0	H	$NHCO_2$-n-Bu	
194	imidazol-2-ylamino	3	0	H	$NHSO_2Ph$	
195	imidazol-2-ylamino	3	0	H	$NHSO_2$-nBu	
196	thiazpl-2-ylamino	3	1	H	NHCbz	

Ex. No.	R^1-U	m	n	R^8	R^9	MS
197	2-aminopyridin-6-yl	3	1	H	$NHCO_2$-n-Bu	
198	2-aminopyridin-6-yl	3	1	H	$NHSO_2Ph$	
199	2-aminopyridin-6-yl	3	1	H	$NHSO_2$-nBu	

200	2-aminopyridin-6-yl	4	0	H	NHCbz	
201	2-aminopyridin-6-yl	4	0	H	$NHCO_2$-n-Bu	
202	2-aminopyridin-6-yl	4	0	H	$NHSO_2Ph$	
203	2-aminopyridin-6-yl	4	0	H	$NHSO_2$-nBu	
204	2-aminopyridin-6-yl	3	0	H	NHCbz	
205	2-aminopyridin-6-yl	3	0	H	$NHCO_2$-n-Bu	
206	2-amihopyridin-6-yl	3	0	H	$NHSO_2Ph$	
207	2-aminopyridin-6-yl	3	0	H	$NHSO_2$-nBu	
208	2-aminopyridin-3-yl	2	0	H	NHCbz	
209	2-aminopyridin-3-yl	2	0	H	$NHCO_2$-n-Bu	
210	2-aminopyridin-3-yl	2	0	H	$NHSO_2Ph$	
211	2-aminopyridin-3-yl	2	0	H	$NHSO_2$-nBu	
212	2-aminothiazol-4-yl	3	1	H	NHCbz	
213	2-aminothiazol-4-yl	3	1	H	$NHCO_2$-n-Bu	
214	2-aminothiazol-4-yl	3	1	H	$NHSO_2Ph$	
215	2-aminothiazol-4-yl	3	1	H	$NHSO_2$-nBu	
216	2-aminothiazol-4-yl	4	0	H	NHCbz	
Ex. No.	R^1-U	m	n	R^8	R^9	MS
217	2-aminothiazol-4-yl	4	0	H	$NHCO_2$-n-Bu	
218	2-aminothiazol-4-yl	4	0	H	$NHSO_2Ph$	
219	2-aminopyridin-6-yl	4	0	H	$NHSO_2$-nBu	
220	2-aminothiazol-4-yl	3	0	H	NHCbz	
221	2-aminothiazol-4-yl	3	0	H	$NHCO_2$-n-Bu	
222	2-aminothiazol-4-yl	3	0	H	$NHSO_2Ph$	

223	2-aminothiazol-4-yl	3	0	H	$NHSO_2$-nBu	
224	2-aminothiazol-4-yl	3	1	H	NHCbz	
225	2-aminothiazol-4-yl	3	1	H	$NHCO_2$-n-Bu	
226	1,3,4-thiadiazol-2-ylamino	3	1	H	$NHSO_2Ph$	
227	1,3,4-thiadiazol-2-ylamino	3	1	H	$NHSO_2$-nBu	
228	1,3,4-thiadiazol-2-ylamino	4	0	H	NHCbz	
229	1,3,4-thiadiazol-2-ylamino	4	0	H	$NHCO_2$-n-Bu	
230	1,3,4-thiadiazol-2-ylamino	4	0	H	$NHSO_2Ph$	
231	1,3,4-thiadiazol-2-ylamino	4	0	H	$NHSO_2$-nBu	
232	1,3,4-thiadiazol-2-ylamino	3	0	H	NHCbz	
233	1,3,4-thiadiazol-2-ylamino	3	0	H	$NHCO_2$-n-Bu	
234	1,3,4-thiadiazol-2-ylamino	3	0	H	$NHSO_2Ph$	
235	1,2,4-thiadiazol-5-ylamino	3	0	H	$NHSO_2$-nBu	
236	1,2,4-thiadiazol-5-ylamino	3	1	H	NHCbz	
Ex. No.	R^1-U	m	n	R^8	R^9	MS
237	1,2,4-thiadiazol-5-ylamino	3	1	H	$NHCO_2$-n-Bu	
238	1,2,4-thiadiazol-5-ylamino	3	1	H	$NHSO_2Ph$	
239	1,2,4-thiadiazol-5-ylamino	3	1	H	$NHSO_2$-nBu	
240	1,2,4-thiadiazol-5-ylamino	4	0	H	NHCbz	
241	1,2,4-thiadiazol-5-ylamino	4	0	H	$NHCO_2$-n-Bu	
242	1,2,4-thiadiazol-5-ylamino	4	0	H	$NHSO_2Ph$	
243	1,2,4-thiadiazol-5-ylamino	4	0	H	$NHSO_2$-nBu	
244	1,2,4-thiadiazol-5-ylamino	3	0	H	NHCbz	
245	1,2,4-thiadiazol-5-ylamino	3	0	H	$NHCO_2$-n-Bu	

Ex. No.	R^1-U	m	n	R^8	R^9	MS
246	1,2,4-thiadiazol-5-ylamino	3	0	H	$NHSO_2Ph$	
247	isoxazol-3-ylamino	3	0	H	$NHSO_2$-nBu	
248	isoxazol-3-ylamino	3	1	H	NHCbz	
249	isoxazol-3-ylamino	3	1	H	$NHCO_2$-n-Bu	
250	isoxazol-3-ylamino	3	1	H	$NHSO_2Ph$	
251	isoxazol-3-ylamino	3	1	H	$NHSO_2$-nBu	
252	isoxazol-3-ylamino	4	0	H	NHCbz	
253	isoxazol-3-ylamino	4	0	H	$NHCO_2$-n-Bu	
254	isoxazol-3-ylamino	4	0	H	$NHSO_2Ph$	
255	isoxazol-3-ylamino	4	0	H	$NHSO_2$-nBu	
256	isoxazol-3-ylamino	3	0	H	NHCbz	
257	isoxazol-3-ylamino	3	0	H	$NHCO_2$-n-Bu	
258	isoxazol-3-ylamino	3	0	H	$NHSO_2Ph$	
259	oxazol-2-ylamino	3	0	H	$NHSO_2$-nBu	
260	oxazol-2-ylamino	3	1	H	NHCbz	
261	oxazol-2-ylamino	3	1	H	$NHCO_2$-n-Bu	
262	oxazol-2-ylamino	3	1	H	$NHSO_2Ph$	
263	oxazol-2-ylamino	3	1	H	$NHSO_2$-nBu	
264	oxazol-2-ylamino	4	0	H	NHCbz	
265	oxazol-2-ylamino	4	0	H	$NHCO_2$-n-Bu	
266	oxazol-2-ylamino	4	0	H	$NHSO_2Ph$	
267	oxazol-2-ylamino	4	0	H	$NHSO_2$-nBu	
268	oxazol-2-ylamino	3	0	H	NHCbz	

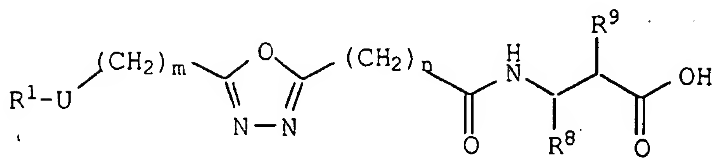
269	oxazol-2-ylamino	3	0	H	$NHCO_2$-n-Bu	
270	oxazol-2-ylamino	3	0	H	$NHSO_2Ph$	
271	oxazol-2-ylamino	3	0	H	$NHSO_2$-nBu	
272	1,2,5-thiadiazol-3-ylamino	3	1	H	NHCbz	
273	1,2,5-thiadiazol-3-ylamino	3	1	H	$NHCO_2$-n-Bu	
274	1,2,5-thiadiazol-3-ylamino	3	1	H	$NHSO_2Ph$	
275	1,2,5-thiadiazol-3-ylamino	3	1	H	$NHSO_2$-nBu	
276	1,2,5-thiadiazol-3-ylamino	4	0	H	NHCbz	
Ex. No.	R^1-U	m	n	R^8	R^9	MS
277	1,2,5-thiadiazol-3-ylamino	4	0	H	$NHCO_2$-n-Bu	
278	1,2,5-thiadiazol-3-ylamino	4	0	H	$NHSO_2Ph$	
279	1,2,5-thiadiazol-3-ylamino	4	0	H	$NHSO_2$-nBu	
280	1,2,5-thiadiazol-3-ylamino	3	0	H	NHCbz	
281	1,2,5-thiadiazol-3-ylamino	3	0	H	$NHCO_2$-n-Bu	
282	1,2,5-thiadiazol-3-ylamino	3	0	H	$NHSO_2Ph$	
283	1,2,5-thiadiazol-3-ylamino	3	0	H	$NHSO_2$-nBu	
284	imidazolin-2-ylamino	2	2	H	NHCbz	
285	imidazolin-2-ylamino	2	2	H	$NHCO_2$-n-Bu	
286	imidazolin-2-ylamino	2	2	H	$NHSO_2Ph$	
287	imidazolin-2-ylamino	2	2	H	$NHSO_2$-nBu	
288	tetrahydropyrimidin-2-ylamino	2	2	H	NHCbz	
289	tetrahydropyrimidin-2-ylamino	2	2	H	$NHCO_2$-n-Bu	
290	tetrahydropyrimidin-2-ylamino	2	2	H	$NHSO_2Ph$	
291	tetrahydropyrimidin-2-ylamino	2	2	H	$NHSO_2$-nBu	

Ex. No.	R^1-U	m	n	R^8	R^9	MS
292	benzimidazol-2-ylamino	4	0	H	NHCbz	
293	benzthiazol-2-ylamino	4	0	H	NHCbz	
294	1,2-pyrazol-3-ylamino	4	0	H	NHCbz	
295	1,2,4-triazol-5-ylamino	4	0	H	NHCbz	
296	imidazol-4-ylamino	4	0	H	NHCbz	
297	1,3,4-oxadiazol-2-ylamino	4	0	H	NHCbz	
298	1,2,4-thiadiazol-5-ylamino	4	0	H	NHCbz	
299	1,2,4-thiadiazol-3-ylamino	4	0	H	NHCbz	
300	1,2,5-oxadiazol-3-ylamino	4	0	H	NHCbz	
301	1,2,4-oxadiazol-5-ylamino	4	0	H	NHCbz	
302	1,2,4-oxadiazol-3-ylamino	4	0	H	NHCbz	
303	2-iminopyrrolidin-5-yl	3	1	H	NHCbz	
304	2-imihopyrrolidin-5-yl	3	1	H	$NHSO_2Ph$	
305	2-iminopyrrolidin-5-yl	3	0	H	NHCbz	
306	2-iminopyrrolidin-5-yl	3	0	H	$NHSO_2Ph$	
307	2-iminopyrrolidin-5-yl	2	1	H	NHCbz	
308	2-iminopyrrolidin-5-yl	2	1	H	$NHSO_2Ph$	
309	2-iminopiperidin-6-yl	3	1	H	NHCbz	
310	2-iminopiperidin-6-yl	3	1	H	$NHSO_2Ph$	
311	2-iminopiperidin-6-yl	3	0	H	NHCbz	
312	2-iminopiperidin-6-yl	3	0	H	$NHSO_2Ph$	
313	2-iminopiperidin-6-yl	2	1	H	NHCbz	
314	2-iminopiperidin-6-yl	2	1	H	$NHSO_2Ph$	

315	2-iminoazepin-7-yl	3	1	H	NHCbz	
316	2-iminoazepin-7-yl	3	1	H	$NHSO_2Ph$	

Ex. No.	R^1-U	m	n	R^8	R^9	MS
317	2-iminoazepin-7-yl	3	0	H	NHCbz	
318	2-iminoazepin-7-yl	3	0	H	$NHSO_2Ph$	
319	2-iminoazepin-7-yl	2	1	H	NHCbz	
320	2-iminoazepin-7-yl	2	1	H	$NHSO_2Ph$	
321	imidazolin-2-ylamino	4	0	H	NHCbz	491
322	benzthiazol-2-ylamino	4	0	n-Bu	H	
323	1,2-pyrazol-3-ylamino	4	0	n-Bu	H	
324	1,2,4-triazol-5-ylamino	4	0	n-Bu	H	
325	imidazol-4-ylamino	4	0	n-Bu	H	
326	1,3,4-oxadiazol-2-ylamino	4	0	n-Bu	H	
327	imidazolin-2-ylamino	4	0	H	(2,4,6-trimethylphenylsulfonyl)amino	538
328	1,2,4-thiadiazol-3-ylamino	4	0	n-Bu	H	
329	1,2,5-oxadiazol-3-ylamino	4	0	n-Bu	H	
330	imidazolin-2-ylamino	4	0	H	(1-naphthalenesulphonylamino	546
331	1,2,4-oxadiazol-3-ylamino	4	0	n-Bu	H	

Table 2



Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
501	tetrahydropyrimidin -2-ylamino	3	1	H	H	
502	tetrahydropyrimidin -2-ylamino	3	1	H	NHCbz	
503	tetrahydropyrimidin -2-ylamino	3	1	H	NHtBOC	
504	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2$-nBu	
505	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2Et$	
506	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2Me$	
507	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO(CH_2)_nPh$	
508	tetrahydropyrimidin -2-ylamino	3	1	H	NHCOtBu	
509	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO-n-C_5H_{11}	
510	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO-n-C_4H_9	
511	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_2CH_3$	
512	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_3$	
513	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2CH_3$	
514	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2CH_2CH_3$	
515	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2$n-Bu	
516	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2Ph$	
517	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	

518	tetrahydropyrimidin -2-ylamino	3	1	H	$NHSO_2Bn$	
519	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO(2-pyridyl)	
520	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO(3-pyridyl)	
521	tetrahydropyrimidin -2-ylamino	3	1	H	NHCO(4-pyridyl)	
522	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_2$(2-pyridyl)	
523	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_2$(3-pyridyl)	
524	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCOCH_2$(4-pyridyl)	
525	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2CH_2$(2-pyridyl)	
526	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2CH_2$(3-pyridyl)	
527	tetrahydropyrimidin -2-ylamino	3	1	H	$NHCO_2CH_2$(4-pyridyl)	
528	imidazolin-2-ylamino	3	1	H	H	
529	imidazolin-2-ylamino	3	1	H	NHCbz	
530	imidazolin-2-ylamino	3	1	H	NHtBOC	
531	imidazolin-2-ylamino	3	1	H	$NHCO_2$-nBu	
532	imidazolin-2-ylamino	3	1	H	$NHCO_2Et$	
533	imidazolin-2-ylamino	3	1	H	$NHCO_2Me$	
534	imidazolin-2-ylamino	3	1	H	$NHCO(CH_2)_nPh$	
535	imidazolin-2-ylamino	3	1	H	NHCOtBu	
Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
536	imidazolin-2-ylamino	3	1	H	NHCO-n-C_5H_{11}	
537	imidazolin-2-ylamino	3	1	H	NHCO-n-C_4H_9	
538	imidazolin-2-ylamino	3	1	H	$NHCOCH_2CH_3$	
539	imidazolin-2-ylamino	3	1	H	$NHCOCH_3$	
540	imidazolin-2-ylamino	3	1	H	$NHSO_2CH_3$	

Ex. No.	R^1–U	m	n	R^8	R^{16}	MS
541	imidazolin-2-ylamino	3	1	H	$NHSO_2CH_2CH_3$	
542	imidazolin-2-ylamino	3	1	H	$NHSO_2$n-Bu	
543	imidazolin-2-ylamino	3	1	H	$NHSO_2Ph$	
544	imidazolin-2-ylamino	3	1	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	
545	imidazolin-2-ylamino	3	1	H	$NHSO_2Bn$	
546	imidazolin-2-ylamino	3	1	H	NHCO(2-pyridyl)	
547	imidazolin-2-ylamino	3	1	H	NHCO(3-pyridyl)	
548	imidazolin-2-ylamino	3	1	H	NHCO(4-pyridyl)	
549	imidazolin-2-ylamino	3	1	H	$NHCOCH_2$(2-pyridyl)	
550	imidazolin-2-ylamino	3	1	H	$NHCOCH_2$(3-pyridyl)	
551	imidazolin-2-ylamino	3	1	H	$NHCOCH_2$(4-pyridyl)	
552	imidazolin-2-ylamino	3	1	H	$NHCO_2CH_2$(2-pyridyl)	
553	imidazolin-2-ylamino	3	1	H	$NHCO_2CH_2$(3-pyridyl)	
554	imidazolin-2-ylamino	3	1	H	$NHCO_2CH_2$(4-pyridyl)	
555	tetrahydropyrimidin-2-ylamino	4	0	H	H	
Ex. No.	**R^1–U**	**m**	**n**	**R^8**	**R^{16}**	**MS**
556	tetrahydropyrimidin-2-ylamino	4	0	H	NHCbz	
557	tetrahydropyrimidin-2-ylamino	4	0	H	NHtBOC	
558	tetrahydropyrimidin-2-ylamino	4	0	H	$NHCO_2$-nBu	
559	tetrahydropyrimidin-2-ylamino	4	0	H	$NHCO_2Et$	
560	tetrahydropyrimidin-2-ylamino	4	0	H	$NHCO_2Me$	
561	tetrahydropyrimidin-2-ylamino	4	0	H	$NHCO(CH_2)_nPh$	
562	tetrahydropyrimidin-2-ylamino	4	0	H	NHCOtBu	
563	tetrahydropyrimidin-2-ylamino	4	0	H	NHCO-n-C_5H_{11}	

564	tetrahydropyrimidin -2-ylamino	4	0	H	NHCO-n-C_4H_9	
565	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_2CH_3$	
566	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_3$	
567	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2CH_3$	
568	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2CH_2CH_3$	
569	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2$n-Bu	
570	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2Ph$	
571	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	
572	tetrahydropyrimidin -2-ylamino	4	0	H	$NHSO_2Bn$	
573	tetrahydropyrimidin -2-ylamino	4	0	H	NHCO(2-pyridyl)	
574	tetrahydropyrimidin -2-ylamino	4	0	H	NHCO(3-pyridyl)	
575	tetrahydropyrimidin -2-ylamino	4	0	H	NHCO(4-pyridyl)	
Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
576	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_2$(2-pyridyl)	
577	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_2$(3-pyridyl)	
578	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCOCH_2$(4-pyridyl)	
579	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCO_2CH_2$(2-pyridyl)	
580	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCO_2CH_2$(3-pyridyl)	
581	tetrahydropyrimidin -2-ylamino	4	0	H	$NHCO_2CH_2$(4-pyridyl)	
582	imidazolin-2-ylamino	4	0	H	H	
583	imidazolin-2-ylamino	4	0	H	NHCbz	
584	imidazolin-2-ylamino	4	0	H	NHtBOC	
585	imidazolin-2-ylamino	4	0	H	$NHCO_2$-nBu	
586	imidazolin-2-ylamino	4	0	H	$NHCO_2Et$	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
587	imidazolin-2-ylamino	4	0	H	$NHCO_2Me$	
588	imidazolin-2-ylamino	4	0	H	$NHCO(CH_2)_nPh$	
589	imidazolin-2-ylamino	4	0	H	NHCOtBu	
590	imidazolin-2-ylamino	4	0	H	NHCO-n-C_5H_{11}	
591	imidazolin-2-ylamino	4	0	H	NHCO-n-C_4H_9	
592	imidazolin-2-ylamino	4	0	H	$NHCOCH_2CH_3$	
593	imidazolin-2-ylamino	4	0	H	$NHCOCH_3$	
594	imidazolin-2-ylamino	4	0	H	$NHSO_2CH_3$	
595	imidazolin-2-ylamino	4	0	H	$NHSO_2CH_2CH_3$	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
596	imidazolin-2-ylamino	4	0	H	$NHSO_2$n-Bu	
597	imidazolin-2-ylamino	4	0	H	$NHSO_2Ph$	
598	imidazolin-2-ylamino	4	0	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	
599	imidazolin-2-ylamino	4	0	H	$NHSO_2Bn$	
600	imidazolin-2-ylamino	4	0	H	NHCO(2-pyridyl)	
601	imidazolin-2-ylamino	4	0	H	NHCO(3-pyridyl)	
602	imidazolin-2-ylamino	4	0	H	NHCO(4-pyridyl)	
603	imidazolin-2-ylamino	4	0	H	$NHCOCH_2$(2-pyridyl)	
604	imidazolin-2-ylamino	4	0	H	$NHCOCH_2$(3-pyridyl)	
605	imidazolin-2-ylamino	4	0	H	$NHCOCH_2$(4-pyridyl)	
606	imidazolin-2-ylamino	4	0	H	$NHCO_2CH_2$(2-pyridyl)	
607	imidazolin-2-ylamino	4	0	H	$NHCO_2CH_2$(3-pyridyl)	
608	imidazolin-2-ylamino	4	0	H	$NHCO_2CH_2$(4-pyridyl)	
609	tetrahydropyrimidin-2-ylamino	3	0	H	H	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
610	tetrahydropyrimidin -2-ylamino	3	0	H	NHCbz	
611	tetrahydropyrimidin -2-ylamino	3	0	H	NHtBOC	
612	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2$-nBu	
613	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2Et$	
614	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2Me$	
615	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO(CH_2)_nPh$	
616	tetrahydropyrimidin -2-ylamino	3	0	H	NHCOtBu	
617	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO-n-C_5H_{11}	
618	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO-n-C_4H_9	
619	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_2CH_3$	
620	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_3$	
621	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2CH_3$	
622	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2CH_2CH_3$	
623	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2$n-Bu	
624	tetrahydropyrimidin -2-ylamino	3	0		$NHSO_2Ph$	
625	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	
626	tetrahydropyrimidin -2-ylamino	3	0	H	$NHSO_2Bn$	
627	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO(2-pyridyl)	
628	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO(3-pyridyl)	
629	tetrahydropyrimidin -2-ylamino	3	0	H	NHCO(4-pyridyl)	
630	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_2$(2-pyridyl)	
631	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_2$(3-pyridyl)	
632	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCOCH_2$(4-pyridyl)	

633	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2CH_2$(2-pyridyl)	
634	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2CH_2$(3-pyridyl)	
635	tetrahydropyrimidin -2-ylamino	3	0	H	$NHCO_2CH_2$(4-pyridyl)	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
636	imidazolin-2-ylamino	3	0	H	H	
637	imidazolin-2-ylamino	3	0	H	NHCbz	
638	imidazolin-2-ylamino	3	0	H	NHtBOC	
639	imidazolin-2-ylamino	3	0	H	$NHCO_2$-nBu	
640	imidazolin-2-ylamino	3	0	H	$NHCO_2Et$	
641	imidazolin-2-ylamino	3	0	H	$NHCO_2Me$	
642	imidazolin-2-ylamino	3	0	H	$NHCO(CH_2)_nPh$	
643	imidazolin-2-ylamino	3	0	H	NHCOtBu	
644	imidazolin-2-ylamino	3	0	H	NHCO-n-C_5H_{11}	
645	imidazolin-2-ylamino	3	0	H	NHCO-n-C_4H_9	
646	imidazolin-2-ylamino	3	0	H	$NHCOCH_2CH_3$	
647	imidazolin-2-ylamino	3	0	H	$NHCOCH_3$	
648	imidazolin-2-ylamino	3	0	H	$NHSO_2CH_3$	
649	imidazolin-2-ylamino	3	0	H	$NHSO_2CH_2CH_3$	
650	imidazolin-2-ylamino	3	0	H	$NHSO_2$n-Bu	
651	imidazolin-2-ylamino	3	0	H	$NHSO_2Ph$	
652	imidazolin-2-ylamino	3	0	H	$NHSO_2C_6H_4(4\text{-}CH_3)$	
653	imidazolin-2-ylamino	3	0	H	$NHSO_2Bn$	
654	imidazolin-2-ylamino	3	0	H	NHCO(2-pyridyl)	
655	imidazolin-2-ylamino	3	0	H	NHCO(3-pyridyl)	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
656	imidazolin-2-ylamino	3	0	H	NHCO(4-pyridyl)	
657	imidazolin-2-ylamino	3	0	H	$NHCOCH_2$(2-pyridyl)	
658	imidazolin-2-ylamino	3	0	H	$NHCOCH_2$(3-pyridyl)	
659	imidazolin-2-ylamino	3	0	H	$NHCOCH_2$(4-pyridyl)	
660	imidazolin-2-ylamino	3	0	H	$NHCO_2CH_2$(2-pyridyl)	
661	imidazolin-2-ylamino	3	0	H	$NHCO_2CH_2$(3-pyridyl)	
662	imidazolin-2-ylamino	3	0	H	$NHCO_2CH_2$(4-pyridyl)	
663	pyridin-2-ylamino	3	1	H	NHCbz	
664	pyridin-2-ylamino	3	1	H	$NHCO_2$-n-Bu	
665	pyridin-2-ylamino	3	1	H	$NHSO_2Ph$	
666	pyridin-2-ylamino	3	1	H	$NHSO_2$-nBu	
667	pyridin-2-ylamino	4	0	H	NHCbz	
668	pyridin-2-ylamino	4	0	H	$NHCO_2$-n-Bu	
669	pyridin-2-ylamino	4	0	H	$NHSO_2Ph$	
670	pyridin-2-ylamino	4	0	H	$NHSO_2$-nBu	
671	pyridin-2-ylamino	3	0	H	NHCbz	
672	pyridin-2-ylamino	3	0	H	$NHCO_2$-n-Bu	
673	pyridin-2-ylamino	3	0	H	$NHSO_2Ph$	
674	pyridin-2-ylamino	3	0	H	$NHSO_2$-nBu	
675	imidazol-2-ylamino	3	1	H	NHCbz	
Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
676	imidazol-2-ylamino	3	1	H	$NHCO_2$-n-Bu	
677	imidazol-2-ylamino	3	1	H	$NHSO_2Ph$	

678	imidazol-2-ylamino	3	1	H	$NHSO_2$-nBu	
679	imidazol-2-ylamino	4	0	H	NHCbz	
680	imidazol-2-ylamino	4	0	H	$NHCO_2$-n-Bu	
681	imidazol-2-ylamino	4	0	H	$NHSO_2Ph$	
682	imidazol-2-ylamino	4	0	H	$NHSO_2$-nBu	
683	imidazol-2-ylamino	3	0	H	NHCbz	
684	imidazol-2-ylamino	3	0	H	$NHCO_2$-n-Bu	
685	imidazol-2-ylamino	3	0	H	$NHSO_2Ph$	
686	imidazol-2-ylamino	3	0	H	$NHSO_2$-nBu	
687	thiazol-2-ylamino	3	1	H	NHCbz	
688	2-aminopyridin-6-yl	3	1	H	$NHCO_2$-n-Bu	
689	2-aminopyridin-6-yl	3	1	H	$NHSO_2Ph$	
690	2-aminopyridin-6-yl	3	1	H	$NHSO_2$-nBu	
691	2-aminopyridin-6-yl	4	0	H	NHCbz	
692	2-aminopyridin-6-yl	4	0	H	$NHCO_2$-n-Bu	
693	2-aminopyridin-6-yl	4	0	H	$NHSO_2Ph$	
694	2-aminopyridin-6-yl	4	0	H	$NHSO_2$-nBu	
695	2-aminopyridin-6-yl	3	0	H	NHCbz	
Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
696	2-aminopyridin-6-yl	3	0	H	$NHCO_2$-n-Bu	
697	2-aminopyridin-6-yl	3	0	H	$NHSO_2Ph$	
698	2-aminopyridin-6-yl	3	0	H	$NHSO_2$-nBu	
699	2-aminopyridin-3-yl	2	0	H	NHCbz	
700	2-aminopyridin-3-yl	2	0	H	$NHCO_2$-n-Bu	

701	2-aminopyridin-3-yl	2	0	H	$NHSO_2Ph$	
702	2-aminopyridin-3-yl	2	0	H	$NHSO_2$-nBu	
703	2-aminothiazol-4-yl	3	1	H	NHCbz	
704	2-aminothiazol-4-yl	3	1	H	$NHCO_2$-n-Bu	
705	2-aminothiazol-4-yl	3	1	H	$NHSO_2Ph$	
706	2-aminothiazol-4-yl	3	1	H	$NHSO_2$-nBu	
707	2-aminothiazol-4-yl	4	0	H	NHCbz	
708	2-aminothiazol-4-yl	4	0	H	$NHCO_2$-n-Bu	
709	2-aminothiazol-4-yl	4	0	H	$NHSO_2Ph$	
710	2-aminopyridin-6-yl	4	0	H	$NHSO_2$-nBu	
711	2-aminothiazol-4-yl	3	0	H	NHCbz	
712	2-aminothiazol-4-yl	3	0	H	$NHCO_2$-n-Bu	
713	2-aminothiazol-4-yl	3	0	H	$NHSO_2Ph$	
714	2-aminothiazol-4-yl	3	0	H	$NHSO_2$-nBu	
715	2-aminothiazol-4-yl	3	1	H	NHCbz	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
716	2-aminothiazol-4-yl	3	1	H	$NHCO_2$-n-Bu	
717	1,3,4-thiadiazol-2-ylamino	3	1	H	$NHSO_2Ph$	
718	1,3,4-thiadiazol-2-ylamino	3	1	H	$NHSO_2$-nBu	
719	1,3,4-thiadiazol-2-ylamino	4	0	H	NHCbz	
720	1,3,4-thiadiazol-2-ylamino	4	0	H	$NHCO_2$-n-Bu	
721	1,3,4-thiadiazol-2-ylamino	4	0	H	$NHSO_2Ph$	
722	1,3,4-thiadiazol-2-ylamino	4	0	H	$NHSO_2$-nBu	
723	1,3,4-thiadiazol-2-ylamino	3	0	H	NHCbz	

724	1,3,4-thiadiazol-2-ylamino	3	0	H	$NHCO_2$-n-Bu	
725	1,3,4-thiadiazol-2-ylamino	3	0	H	$NHSO_2Ph$	
726	1,2,4-thiadiazol-5-ylamino	3	0	H	$NHSO_2$-nBu	
727	1,2,4-thiadiazol-5-ylamino	3	1	H	NHCbz	
728	1,2,4-thiadiazol-5-ylamino	3	1	H	$NHCO_2$-n-Bu	
729	1,2,4-thiadiazol-5-ylamino	3	1	H	$NHSO_2Ph$	
730	1,2,4-thiadiazol-5-ylamino	3	1	H	$NHSO_2$-nBu	
731	1,2,4-thiadiazol-5-ylamino	4	0	H	NHCbz	
732	1,2,4-thiadiazol-5-ylamino	4	0	H	$NHCO_2$-n-Bu	
733	1,2,4-thiadiazol-5-ylamino	4	0	H	$NHSO_2Ph$	
734	1,2,4-thiadiazol-5-ylamino	4	0	H	$NHSO_2$-nBu	
735	1,2,4-thiadiazol-5-ylamino	3	0	H	NHCbz	
Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
736	1,2,4-thiadiazol-5-ylamino	3	0	H	$NHCO_2$-n-Bu	
737	1,2,4-thiadiazol-5-ylamino	3	0	H	$NHSO_2Ph$	
738	isoxazol-3-ylamino	3	0	H	$NHSO_2$-nBu	
739	isoxazol-3-ylamino	3	1	H	NHCbz	
740	isoxazol-3-ylamino	3	1	H	$NHCO_2$-n-Bu	
741	isoxazol-3-ylamino	3	1	H	$NHSO_2Ph$	
742	isoxazol-3-ylamino	3	1	H	$NHSO_2$-nBu	
743	isoxazol-3-ylamino	4	0	H	NHCbz	
744	isoxazol-3-ylamino	4	0	H	$NHCO_2$-n-Bu	
745	isoxazol-3-ylamino	4	0	H	$NHSO_2Ph$	
746	isoxazol-3-ylamino	4	0	H	$NHSO_2$-nBu	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
747	isoxazol-3-ylamino	3	0	H	NHCbz	
748	isoxazol-3-ylamino	3	0	H	$NHCO_2$-n-Bu	
749	isoxazol-3-ylamino	3	0	H	$NHSO_2Ph$	
750	oxazol-2-ylamino	3	0	H	$NHSO_2$-nBu	
751	oxazol-2-ylamino	3	1	H	NHCbz	
752	oxazol-2-ylamino	3	1	H	$NHCO_2$-n-Bu	
753	oxazol-2-ylamino	3	1	H	$NHSO_2Ph$	
754	oxazol-2-ylamino	3	1	H	$NHSO_2$-nBu	
755	oxazol-2-ylamino	4	0	H	NHCbz	
756	oxazol-2-ylamino	4	0	H	$NHCO_2$-n-Bu	
757	oxazol-2-ylamino	4	0	H	$NHSO_2Ph$	
758	oxazol-2-ylamino	4	0	H	$NHSO_2$-nBu	
759	oxazol-2-ylamino	3	0	H	NHCbz	
760	oxazol-2-ylamino	3	0	H	$NHCO_2$-n-Bu	
761	oxazol-2-ylamino	3	0	H	$NHSO_2Ph$	
762	oxazol-2-ylamino	3	0	H	$NHSO_2$-nBu	
763	1,2,5-thiadiazol-3-ylamino	3	1	H	NHCbz	
764	1,2,5-thiadiazol-3-ylamino	3	1	H	$NHCO_2$-n-Bu	
765	1,2,5-thiadiazol-3-ylamino	3	1	H	$NHSO_2Ph$	
766	1,2,5-thiadiazol-3-ylamino	3	1	H	$NHSO_2$-nBu	
767	1,2,5-thiadiazol-3-ylamino	4	0	H	NHCbz	
768	1,2,5-thiadiazol-3-ylamino	4	0	H	$NHCO_2$-n-Bu	
769	1,2,5-thiadiazol-3-ylamino	4	0	H	$NHSO_2Ph$	

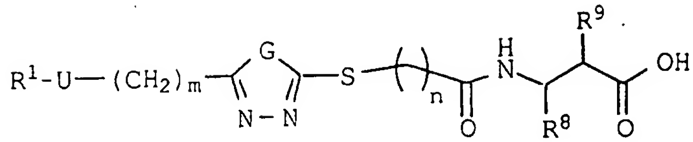
770	1,2,5-thiadiazol-3-ylamino	4	0	H	$NHSO_2$-nBu	
771	1,2,5-thiadiazol-3-ylamino	3	0	H	NHCbz	
772	1,2,5-thiadiazol-3-ylamino	3	0	H	$NHCO_2$-n-Bu	
773	1,2,5-thiadiazol-3-ylamino	3	0	H	$NHSO_2Ph$	
774	1,2,5-thiadiazol-3-ylamino	3	0	H	$NHSO_2$-nBu	
775	imidazolin-2-ylamino	2	2	H	NHCbz	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
776	imidazolin-2-ylamino	2	2	H	$NHCO_2$-n-Bu	
777	imidazolin-2-ylamino	2	2	H	$NHSO_2Ph$	
778	imidazolin-2-ylamino	2	2	H	$NHSO_2$-nBu	
779	tetrahydropyrimidin-2-ylamino	2	2	H	NHCbz	
780	tetrahydropyrimidin-2-ylamino	2	2	H	$NHCO_2$-n-Bu	
781	tetrahydropyrimidin-2-ylamino	2	2	H	$NHSO_2Ph$	
782	tetrahydropyrimidin-2-ylamino	2	2	H	$NHSO_2$-nBu	
783	benzimidazol-2-ylamino	4	0	H	NHCbz	
784	benzthiazol-2-ylamino	4	0	H	NHCbz	
785	1,2-pyrazol-3-ylamino	4	0	H	NHCbz	
786	1,2,4-triazol-5-ylamino	4	0	H	NHCbz	
787	imidazol-4-ylamino	4	0	H	NHCbz	
788	1,3,4-oxadiazol-2-ylamino	4	0	H	NHCbz	
789	1,2,4-thiadiazol-5-ylamino	4	0	H	NHCbz	
790	1,2,4-thiadiazol-3-ylamino	4	0	H	NHCbz	
791	1,2,5-oxadiazol-3-ylamino	4	0	H	NHCbz	
792	1,2,4-oxadiazol-5-ylamino	4	0	H	NHCbz	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
793	1,2,4-oxadiazol-3-ylamino	4	0	H	NHCbz	
794	2-iminopyrrolidin-5-yl	3	1	H	NHCbz	
795	2-iminopyrrolidin-5-yl	3	1	H	$NHSO_2Ph$	
796	2-iminopyrrolidin-5-yl	3	0	H	NHCbz	
797	2-iminopyrrolidin-5-yl	3	0	H	$NHSO_2Ph$	
798	2-iminopyrrolidin-5-yl	2	1	H	NHCbz	
799	2-iminopyrrolidin-5-yl	2	1	H	$NHSO_2Ph$	
800	2-iminopiperidin-6-yl	3	1	H	NHCbz	
801	2-iminopiperidin-6-yl	3	1	H	$NHSO_2Ph$	
802	2-iminopiperidin-6-yl	3	0	H	NHCbz	
803	2-iminopiperidin-6-yl	3	0	H	$NHSO_2Ph$	
804	2-iminopiperidin-6-yl	2	1	H	NHCbz	
805	2-iminopiperidin-6-yl	2	1	H	$NHSO_2Ph$	
806	2-iminoazepin-7-yl	3	1	H	NHCbz	
807	2-iminoazepin-7-yl	3	1	H	$NHSO_2Ph$	
808	2-iminoazepin-7-yl	3	0	H	NHCbz	
809	2-iminoazepin-7-yl	3	0	H	$NHSO_2Ph$	
810	2-iminoazepin-7-yl	2	1	H	NHCbz	
811	2-iminoazepin-7-yl	2	1	H	$NHSO_2Ph$	
812	benzimidazol-2-ylamino	4	0	n-Bu	H	
813	benzthiazol-2-ylamino	4	0	n-Bu	H	
814	1,2-pyrazol-3-ylamino	4	0	n-Bu	H	
815	1,2,4-triazol-5-ylamino	4	0	n-Bu	H	

Ex. No.	R^1-U	m	n	R^8	R^{16}	MS
816	imidazol-4-ylamino	4	0	n-Bu	H	
817	1,3,4-oxadiazol-2-ylamino	4	0	n-Bu	H	
818	1,2,4-thiadiazol-5-ylamino	4	0	n-Bu	H	
819	1,2,4-thiadiazol-3-ylamino	4	0	n-Bu	H	
820	1,2,5-oxadiazol-3-ylamino	4	0	n-Bu	H	
821	1,2,4-oxadiazol-5-ylamino	4	0	n-Bu	H	
822	1,2,4-oxadiazol-3-ylamino	4	0	n-Bu	H	

Table 3



Ex. No.	R^1-U	m	n	G	R^8	R^9
1001	imidazolin-2-ylamino	3	0	O	H	H
1002	imidazolin-2-ylamino	2	0	O	H	H
1003	imidazolin-2-ylamino	2	0	O	H	NHCbz
1004	imidazolin-2-ylamino	3	0	O	H	NHCbz
1005	imidazolin-2-ylamino	2	0	S	H	NHCbz
1006	imidazolin-2-ylamino	3	0	S	H	NHCbz
1009	tetrahydropyrimidin-2-ylamino	2	0	O	H	H
1010	tetrahydropyrimidin-2-ylamino	2	0	O	H	NHCbz
1011	tetrahydropyrimidin-2-ylamino	3	0	O	H	H
1012	tetrahydropyrimidin-2-ylamino	3	0	O	H	NHCbz
1013	tetrahydropyrimidin-2-ylamino	2	0	S	H	NHCbz
1014	tetrahydropyrimidin-2-ylamino	3	0	S	H	NHCbz
1015	tetrahydropyrimidin-2-ylamino	2	0	O	H	NHCbz
1017	imidazolin-2-ylamino	2	0	O	H	NH-*n*-Bu
1018	imidazolin-2-ylamino	3	0	O	H	NH-*n*-Bu
1019	imidazolin-2-ylamino	2	0	S	H	NH-*n*-Bu
1020	imidazolin-2-ylamino	3	0	S	H	NH-*n*-Bu
1023	tetrahydropyrimidin-2-ylamino	2	0	O	H	NH-*n*-Bu
1024	tetrahydropyrimidin-2-ylamino	3	0	O	H	NH-*n*-Bu
1025	tetrahydropyrimidin-2-ylamino	2	0	S	H	NH-*n*-Bu
Ex. No.	R^1-U	m	n	G	R^8	R^9
1026	tetrahydropyrimidin-2-ylamino	3	0	S	H	NH-*n*-Bu
1027	tetrahydropyrimidin-2-ylamino	2	0	S	H	NH-*n*-Bu
1028	tetrahydropyrimidin-2-ylamino	3	0	O	H	NH-*n*-Bu
1029	imidazolin-2-ylamino	2	0	O	H	$NHSO_2Ph(o-CH_3)$
1030	imidazolin-2-ylamino	3	0	O	H	$NHSO_2Ph(o-CH_3)$
1031	imidazolin-2-ylamino	2	0	S	H	$NHSO_2Ph(o-CH_3)$

1032	imidazolin-2-ylamino	3	0	S	H	$NHSO_2Ph(o\text{-}CH_3)$
1033	imidazolin-2-ylamino	2	0	O	H	$NHSO_2Ph(m\text{-}CH_3)$
1034	imidazolin-2-ylamino	3	0	O	H	$NHSO_2Ph(m\text{-}CH_3)$
1035	imidazolin-2-ylamino	2	0	S	H	$NHSO_2Ph(m\text{-}CH_3)$
1036	imidazolin-2-ylamino	3	0	S	H	$NHSO_2Ph(m\text{-}CH_3)$
1037	imidazolin-2-ylamino	2	0	O	H	$NHSO_2Ph(p\text{-}CH_3)$
1038	imidazolin-2-ylamino	3	0	O	H	$NHSO_2Ph(p\text{-}CH_3)$
1039	imidazolin-2-ylamino	2	0	S	H	$NHSO_2Ph(p\text{-}CH_3)$
1040	imidazolin-2-ylamino	3	0	S	H	$NHSO_2Ph(p\text{-}CH_3)$
1041	imidazolin-2-ylamino	2	0	O	H	$SO_2Ph(o\text{-}Cl)$
1042	imidazolin-2-ylamino	3	0	O	H	$SO_2Ph(o\text{-}Cl)$
1043	imidazolin-2-ylamino	2	0	O	H	$SO_2Ph(m\text{-}Cl)$
1044	imidazolin-2-ylamino	3	0	O	H	$SO_2Ph(m\text{-}Cl)$
1045	imidazolin-2-ylamino	2	0	O	H	$SO_2Ph(p\text{-}Cl)$
1046	imidazolin-2-ylamino	3	0	O	H	$SO_2Ph(p\text{-}Cl)$
1047	tetrahydropyrimidin-2-ylamino	2	0	O	H	$SO_2Ph(p\text{-}Cl)$
1048	tetrahydropyrimidin-2-ylamino	3	0	O	H	$SO_2Ph(p\text{-}Cl)$
1049	tetrahydropyrimidin-2-ylamino	2	0	O	H	$SO_2Ph(m\text{-}Cl)$
1050	tetrahydropyrimidin-2-ylamino	3	0	O	H	$SO_2Ph(m\text{-}Cl)$
1051	tetrahydropyrimidin-2-ylamino	2	0	O	H	$SO_2Ph(p\text{-}Cl)$
1052	tetrahydropyrimidin-2-ylamino	3	0	O	H	$SO_2Ph(p\text{-}Cl)$
1053	imidazolin-2-ylamino	2	0	O	H	NHPh(m-F)
1054	imidazolin-2-ylamino	3	0	O	H	NHPh(m-F)
1055	tetrahydropyrimidin-2-ylamino	2	0	O	H	NHPh(m-F)
1056	tetrahydropyrimidin-2-ylamino	3	0	O	H	NHPh(m-F)
1057	imidazolin-2-ylamino	2	0	O	H	NHPh(p-F)
Ex. No.	R^1-U	m	n	G	R^8	R^9
1058	imidazolin-2-ylamino	3	0	O	H	NHPh(p-F)
1059	tetrahydropyrimidin-2-ylamino	2	0	O	H	NHPh(p-F)
1060	tetrahydropyrimidin-2-ylamino	3	0	O	H	NHPh(p-F)
1061	imidazolin-2-ylamino	2	0	O	H	NHPh(m-Br)
1062	imidazolin-2-ylamino	3	0	O	H	NHPh(m-Br)
1063	tetrahydropyrimidin-2-ylamino	2	0	O	H	NHPh(m-Br)
1064	tetrahydropyrimidin-2-ylamino	3	0	O	H	NHPh(m-Br)
1065	imidazolin-2-ylamino	2	0	O	H	$NHSO_2Ph(p\text{-}Br)$
1066	imidazolin-2-ylamino	3	0	O	H	$NHSO_2Ph(p\text{-}Br)$
1067	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHSO_2Ph(p\text{-}Br)$
1068	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHSO_2Ph(p\text{-}Br)$

1069	imidazolin-2-ylamino	2	0	O	H	$NHSO_2Ph(m-OCH_3)$
1070	imidazolin-2-ylamino	3	0	O	H	$NHSO_2Ph(m-OCH_3)$
1071	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHSO_2Ph(m-OCH_3)$
1072	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHSO_2Ph(m-OCH_3)$
1073	imidazolin-2-ylamino	2	0	O	H	$NHSO_2Ph(p-OCH_3)$
1074	imidazolin-2-ylamino	3	0	O	H	$NHSO_2Ph(p-OCH_3)$
1075	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHSO_2Ph(p-OCH_3)$
1076	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHSO_2Ph(p-OCH_3)$
1077	imidazolin-2-ylamino	2	0	O	H	$NHSO_2Bn$
1078	imidazolin-2-ylamino	3	0	O	H	$NHSO_2Bn$
1079	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHSO_2Bn$
1080	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHSO_2Bn$
1081	imidazolin-2-ylamino	2	0	O	H	$NHSO_2Et$
1082	imidazolin-2-ylamino	3	0	O	H	$NHSO_2Et$
1083	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHSO_2Et$
1084	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHSO_2Et$
1085	imidazolin-2-ylamino	2	0	O	H	$NHSO_2$-*n*-Pr
Ex. No.	R^1-U	m	n	Q	R^8	R^9
1086	imidazolin-2-ylamino	3	0	O	H	$NHSO_2$-*n*-Pr
1087	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHSO_2$-*n*-Pr
1088	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHSO_2$-*n*-Pr
1089	imidazolin-2-ylamino	2	0	O	H	$NHSO_2$-*n*-(C_5H_{11})
1090	imidazolin-2-ylamino	3	0	O	H	$NHSO_2$-*n*-(C_5H_{11})
1091	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHSO_2$-*n*-(C_5H_{11})
1092	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHSO_2$-*n*-(C_5H_{11})
1093	imidazolin-2-ylamino	2	0	O	H	$NHCO_2Et$
1094	imidazolin-2-ylamino	3	0	O	H	$NHCO_2Et$
1095	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHCO_2Et$
1096	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHCO_2Et$
1097	imidazolin-2-ylamino	2	0	O	H	$NHCO_2$-*n*-C_5H_{11}
1098	imidazolin-2-ylamino	3	0	O	H	$NHCO_2$-*n*-C_5H_{11}
1099	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHCO_2$-*n*-C_5H_{11}

Ex. No.	R^1-U	m	n	G	R^8	R^9
1100	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHCO_2$-*n*-C_5H_{11}
1101	imidazolin-2-ylamino	4	0	O	H	NHCbz
1102	tetrahydropyrimidin-2-ylamino	4	0	O	H	NHCbz
1103	imidazolin-2-ylamino	4	0	O	H	$NHCO_2$-*n*-Bu
1104	tetrahydropyrimidin-2-ylamino	4	0	O	H	$NHCO_2$-*n*-Bu
1105	imidazolin-2-ylamino	4	0	O	H	$NHSO_2Ph$
1106	tetrahydropyrimidin-2-ylamino	4	0	O	H	$NHSO_2Ph$
1107	imidazolin-2-ylamino	4	0	O	H	$NHSO_2$-*n*-Bu
1108	tetrahydropyrimidin-2-ylamino	4	0	O	H	$NHSO_2$-*n*-Bu
1109	imidazolin-2-ylamino	4	0	S	H	NHCbz
1110	tetrahydropyrimidin-2-ylamino	4	0	S	H	NHCbz
1111	imidazolin-2-ylamino	4	0	S	H	$NHSO_2Bu$
1112	tetrahydropyrimidin-2-ylamino	4	0	S	H	$NHSO_2Bu$
1113	imidazolin-2-ylamino	2	0	O	Me	H
1114	imidazolin-2-ylamino	3	0	O	Me	H

Ex. No.	R^1-U	m	n	G	R^8	R^9
1115	tetrahydropyrimidin-2-ylamino	2	0	O	Me	H
1116	tetrahydropyrimidin-2-ylamino	3	0	O	Me	H
1117	imidazolin-2-ylamino	3	0	S	Me	H
1118	tetrahydropyrimidin-2-ylamino	3	0	S	Me	H
1119	imidazolin-2-ylamino	2	0	O	Me	NHCbz
1120	imidazolin-2-ylamino	3	0	O	Me	NHCbz
1121	tetrahydropyrimidin-2-ylamino	2	0	O	Me	$NHSO_2$-*n*-Bu
1122	tetrahydropyrimidin-2-ylamino	3	0	O	Me	$NHSO_2$-*n*-Bu
1123	imidazolin-2-ylamino	2	0	O	Et	H
1124	imidazolin-2-ylamino	3	0	O	Et	H
1125	tetrahydropyrimidin-2-ylamino	2	0	O	Et	H
1126	tetrahydropyrimidin-2-ylamino	3	0	O	Et	H
1127	imidazolin-2-ylamino	3	0	S	Et	H
1128	tetrahydropyrimidin-2-ylamino	3	0	S	Et	H
1129	imidazolin-2-ylamino	2	0	O	Ph	H
1130	imidazolin-2-ylamino	3	0	O	Ph	H
1131	tetrahydropyrimidin-2-ylamino	2	0	O	Ph	H
1132	tetrahydropyrimidin-2-ylamino	3	0	O	Ph	H
1133	imidazolin-2-ylamino	3	0	S	Ph	H
1134	tetrahydropyrimidin-2-ylamino	3	0	S	Ph	H
1135	imidazolin-2-ylamino	2	0	O	Bn	H

1136	imidazolin-2-ylamino	3	0	O	Bn	H
1137	tetrahydropyrimidin-2-ylamino	2	0	O	Bn	H
1138	tetrahydropyrimidin-2-ylamino	3	0	O	Bn	H
1139	imidazolin-2-ylamino	3	0	S	Bn	H
1140	tetrahydropyrimidin-2-ylamino	3	0	S	Bn	H
1141	imidazolin-2-ylamino	2	0	O	H	NHCbz
1142	imidazolin-2-ylamino	3	0	O	H	NHCbz
1143	tetrahydropyrimidin-2-ylamino	2	0	O	H	NHCbz
1144	tetrahydropyrimidin-2-ylamino	3	0	O	H	NHCbz
Ex. No.	R^1-U	m	n	G	R^8	R^9
1145	imidazolin-2-ylamino	2	0	O	H	$NHSO_2$-*n*-Bu
1146	imidazolin-2-ylamino	3	0	O	H	$NHSO_2$-*n*-Bu
1147	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHSO_2$-*n*-Bu
1148	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHSO_2$-*n*-Bu
1149	imidazolin-2-ylamino	3	0	S	H	NHCbz
1150	tetrahydropyrimidin-2-ylamino	3	0	S	H	NHCbz
1151	imidazolin-2-ylamino	3	0	S	H	$NHSO_2$-*n*-Bu
1152	tetrahydropyrimidin-2-ylamino	3	0	S	H	$NHSO_2$-*n*-Bu
1153	imidazolin-2-ylamino	2	0	O	H	NHCbz
1154	imidazolin-2-ylamino	3	0	O	H	NHCbz
1155	tetrahydropyrimidin-2-ylamino	2	0	O	H	NHCbz
1156	tetrahydropyrimidin-2-ylamino	3	0	O	H	NHCbz
1157	imidazolin-2-ylamino	2	0	O	H	$NHSO_2$-*n*-Bu
1158	imidazolin-2-ylamino	3	0	O	H	$NHSO_2$-*n*-Bu
1159	tetrahydropyrimidin-2-ylamino	2	0	O	H	$NHSO_2$-*n*-Bu
1160	tetrahydropyrimidin-2-ylamino	3	0	O	H	$NHSO_2$-*n*-Bu
1161	imidazolin-2-ylamino	3	0	S	H	NHCbz
1162	tetrahydropyrimidin-2-ylamino	3	0	S	H	NHCbz
1163	imidazolin-2-ylamino	3	0	S	H	$NHSO_2$-*n*-Bu
1164	tetrahydropyrimidin-2-ylamino	3	0	S	H	$NHSO_2$-*n*-Bu
1165	imidazolin-2-ylamino	3	0	O	Me	NHCbz
1166	tetrahydropyrimidin-2-ylamino	3	0	O	Me	$NHSO_2Bu$
1167	imidazolin-2-ylamino	3	0	O	Bn	NHCbz
1168	tetrahydropyrimidin-2-ylamino	3	0	O	Bn	NHCbz
1169	imidazolin-2-ylamino	3	0	O	Me	$NHSO_2$-*n*-Bu
1170	tetrahydropyrimidin-2-ylamino	3	0	O	Me	NHCbz
1171	imidazolin-2-ylamino	3	0	O	Bn	$NHSO_2$-*n*-Bu

Ex. No.	R^1-U	m	n	Q	R^8	R^9
1172	tetrahydropyrimidin-2-ylamino	3	0	O	Bn	NHCbz
1173	(4-oxoimidazolin-2-yl)amino	2	0	O	H	NHCBz
Ex. No.	R^1-U	m	n	G	R^8	R^9
1174	(4-oxoimidazolin-2-yl)amino	3	0	O	H	NHCBz
1175	(4-oxoimidazolin-2-yl)amino	2	0	O	H	$NHCO_2$-*n*-Bu
1176	(4-oxoimidazolin-2-yl)amino	3	0	O	H	$NHCO_2$-*n*-Bu
1177	(4-oxoimidazolin-2-yl)amino	2	0	O	H	$NHSO_2Ph$
1178	(4-oxoimidazolin-2-yl)amino	3	0	O	H	$NHSO_2Ph$
1179	(4-oxoimidazolin-2-yl)amino	2	0	O	H	$NHSO_2$-*n*-Bu
1180	(4-oxoimidazolin-2-yl)amino	3	0	O	H	$NHSO_2$-*n*-Bu
1181	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	O	H	NHCbz
1182	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	O	H	$NHCO_2$-*n*-Bu
1183	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	O	H	$NHSO_2Ph$
1184	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	O	H	$NHSO_2$-*n*-Bu
1185	(4-oxoimidazolin-2-yl)amino	3	0	S	H	NHCbz
1186	(4-oxoimidazolin-2-yl)amino	3	0	S	H	$NHSO_2$-*n*-Bu
1187	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	S	H	NHCbz
1188	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	S	H	$NHSO_2$-*n*-Bu
1189	(4-oxoimidazolin-2-yl)amino	3	0	O	Me	H
1190	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	O	Me	H
1191	(4-oxoimidazolin-2-yl)amino	3	0	O	Bn	H
Ex. No.	R^1-U	m	n	Q	R^8	R^9
1192	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	O	Bn	H

1193	(4-oxoimidazolin-2-yl)amino	3	0	O	Me	NHCbz
1194	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	O	Me	$NHSO_2$-*n*-Bu
1195	(4-oxoimidazolin-2-yl)amino	3	0	O	H	NHCbz
1196	(4-oxotetrahydropyrimidin-2-yl)amino	3	0	O	H	NHCbz
1197	imidazolin-2-ylaminocarbonyl	1	0	O	H	NHCbz
1198	imidazolin-2-ylaminocarbonyl	2	0	O	H	NHCbz
1199	tetrahydropyrimidin-2-ylaminocarbonyl	1	0	O	H	$NHSO_2$-*n*-Bu
1200	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	O	H	$NHSO_2$-*n*-Bu
1201	imidazolin-2-ylaminocarbonyl	2	0	O	H	NHCbz
1202	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	O	H	$NHSO_2$-*n*-Bu
1203	imidazolin-2-ylaminocarbonyl	1	0	O	H	$NHCO_2$-*n*-Bu
1204	imidazolin-2-ylaminocarbonyl	2	0	O	H	$NHCO_2$-*n*-Bu
1205	tetrahydropyrimidin-2-ylaminocarbonyl	1	0	O	H	$NHSO_2Ph$
1206	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	O	H	$NHSO_2Ph$
1207	imidazolin-2-ylaminocarbonyl	2	0	O	Me	NHCbz
1208	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	O	Me	$NHSO_2$-*n*-Bu
1209	imidazolin-2-ylaminocarbonyl	2	0	O	Bn	H
1210	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	O	Bn	H
1211	imidazolin-2-ylaminocarbonyl	2	0	O	Me	H

Ex. No.	R^1-U	m	n	G	R^8	R^9
1212	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	O	Me	H
1213	imidazolin-2-ylaminocarbonyl	2	0	O	H	NHCbz
1214	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	O	H	NHCbz
1215	imidazolin-2-ylaminocarbonyl	2	0	O	H	$NHSO_2$-*n*-Bu
1216	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	O	H	$NHSO_2$-*n*-Bu

1217	imidazolin-2-ylaminocarbonyl	2	0	S	Me	H	
1218	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	S	Bn	H	
1219	imidazolin-2-ylaminocarbonyl	2	0	S	H	NHCbz	
1220	tetrahydropyrimidin-2-ylaminocarbonyl	2	0	S	H	$NHSO_2$-*n*-Bu	
1221	imidazolin-2-ylamino	2	1	O	H	NHCbz	
1222	imidazolin-2-ylamino	3	1	O	H	NHCbz	
1223	tetrahydropyrimidin-2-ylamino	2	1	O	H	NHCbz	
1224	tetrahydropyrimidin-2-ylamino	3	1	O	H	NHCbz	
1225	imidazolin-2-ylamino	2	1	O	H	$NHSO_2$-*n*-Bu	
1226	imidazolin-2-ylamino	3	1	O	H	$NHSO_2$-*n*-Bu	
1227	tetrahydropyrimidin-2-ylamino	2	1	O	H	$NHSO_2$-*n*-Bu	
1228	tetrahydropyrimidin-2-ylamino	3	1	O	H	$NHSO_2$-*n*-Bu	
1229	imidazolin-2-ylamino	2	1	S	H	NHCbz	
1230	imidazolin-2-ylamino	3	1	S	H	NHCbz	
1231	tetrahydropyrimidin-2-ylamino	2	1	S	H	NHCbz	
1232	tetrahydropyrimidin-2-ylamino	3	1	S	H	NHCbz	
1233	imidazolin-2-ylamino	2	1	O	Me	H	
1234	imidazolin-2-ylamino	3	1	O	Me	H	
1235	tetrahydropyrimidin-2-ylamino	2	1	O	Bn	H	
1236	tetrahydropyrimidin-2-ylamino	3	1	O	Bn	H	
Ex. No.	R^1-U	m	n	G	R^8	R^9	
1237	imidazolin-2-ylamino	2	1	S	Me	H	
1238	tetrahydropyrimidin-2-ylamino	2	1	S	Bn	H	
1239	imidazolin-2-ylamino	2	1	O	Me	NHCbz	
1240	tetrahydropyrimidin-2-ylamino	2	1	O	Me	NHCbz	
1241	imidazolin-2-ylamino	2	1	O	H	NHCbz	
1242	tetrahydropyrimidin-2-ylamino	2	1	O	H	NHCbz	
1243	imidazolin-2-ylamino	3	1	O	H	NHCbz	
1244	tetrahydropyrimidin-2-ylamino	3	1	O	H	NHCbz	
1245	pyridin-2-ylamino	2	1	O	H	NHCbz	
1246	imidazol-2-ylamino	2	1	O	H	NHCbz	
1247	1,2,4-thiadiazol-5-ylamino	2	1	O	H	NHCbz	
1248	isoxazol-3-ylamino	2	1	O	H	NHCbz	H

Ex. No.	R^1-U	m	n	G	R^8	R^9
1249	oxazol-2-ylamino	2	1	O	H	NHCbz
1250	1,2,5-thiadiazol-3-ylamino	2	1	O	H	NHCbz
1251	benzimidazol-2-ylamino	2	1	O	H	NHCbz
1252	benzthiazol-2-ylamino	2	1	O	H	NHCbz
1253	1,2-pyrazol-3-ylamino	2	1	O	H	NHCbz
1254	1,2,4-triazol-5-ylamino	2	1	O	H	NHCbz
1255	imidazol-4-ylamino	2	1	O	H	NHCbz
1256	1,3,4-oxadiazol-2-ylamino	2	1	O	H	NHCbz
1257	1,2,4-thiadiazol-5-ylamino	2	1	O	H	NHCbz
1258	1,2,4-thiadiazol-3-ylamino	2	1	O	H	NHCbz
1259	1,2,5-oxadiazol-3-ylamino	2	1	O	H	NHCbz
1260	1,2,4-oxadiazol-5-ylamino	2	1	O	H	NHCbz
1261	1,2,4-oxadiazol-3-ylamino	2	1	O	H	NHCbz
1262	pyridin-2-ylamino	3	0	O	H	NHCbz
1263	imidazol-2-ylamino	3	0	O	H	NHCbz
1264	1,2,4-thiadiazol-5-ylamino	3	0	O	H	NHCbz
Ex. No.	R^1-U	m	n	G	R^8	R^9
1265	isoxazol-3-ylamino	3	0	O	H	NHCbz
1266	oxazol-2-ylamino	3	0	O	H	NHCbz
1267	1,2,5-thiadiazol-3-ylamino	3	0	O	H	NHCbz
1268	benzimidazol-2-ylamino	3	0	O	H	NHCbz
1269	benzthiazol-2-ylamino	3	0	O	H	NHCbz
1270	1,2-pyrazol-3-ylamino	3	0	O	H	NHCbz
1271	1,2,4-triazol-5-ylamino	3	0	O	H	NHCbz
1272	imidazol-4-ylamino	3	0	O	H	NHCbz
1273	1,3,4-oxadiazol-2-ylamino	3	0	O	H	NHCbz
1274	1,2,4-thiadiazol-5-ylamino	3	0	O	H	NHCbz
1275	1,2,4-thiadiazol-3-ylamino	3	0	O	H	NHCbz
1276	1,2,5-oxadiazol-3-ylamino	3	0	O	H	NHCbz
1277	1,2,4-oxadiazol-5-ylamino	3	0	O	H	NHCbz
1278	1,2,4-oxadiazol-3-ylamino	3	0	O	H	NHCbz
1279	pyridin-2-ylamino	2	0	O	H	NHCbz
1280	imidazol-2-ylamino	2	0	O	H	NHCbz
1281	1,2,4-thiadiazol-5-ylamino	2	0	O	H	NHCbz

1282	isoxazol-3-ylamino	2	0	O	H	NHCbz
1283	oxazol-2-ylamino	2	0	O	H	NHCbz
1284	1,2,5-thiadiazol-3-ylamino	2	0	O	H	NHCbz
1285	benzimidazol-2-ylamino	2	0	O	H	NHCbz
1286	benzthiazol-2-ylamino	2	0	O	H	NHCbz
1287	1,2-pyrazol-3-ylamino	2	0	O	H	NHCbz
1288	1,2,4-triazol-5-ylamino	2	0	O	H	NHCbz
1289	imidazol-4-ylamino	2	0	O	H	NHCbz
1290	1,3,4-oxadiazol-2-ylamino	2	0	O	H	NHCbz
1291	1,2,4-thiadiazol-5-ylamino	2	0	O	H	NHCbz
1292	1,2,4-thiadiazol-3-ylamino	2	0	O	H	NHCbz
Ex. No.	R^1-U	m	n	G	R^8	R^9
1293	1,2,5-oxadiazol-3-ylamino	2	0	O	H	NHCbz
1294	1,2,4-oxadiazol-5-ylamino	2	0	O	H	NHCbz
1295	1,2,4-oxadiazol-3-ylamino	2	0	O	H	NHCbz

Utility

The compounds of Formula I of the present invention possess activity as antagonists of integrins such as, for example, the $\alpha_v\beta_3$ or vitronectin receptor, $\alpha_v\beta_5$ or $\alpha_5\beta_1$, and as such have utility in the treatment and diagnosis of cell adhesion, angiogenic disorders, inflammation, bone degradation, cancer metastases, diabetic retinopathy, thrombosis, restenosis, macular degeneration, and other conditions mediated by cell adhesion and/or cell migration and/or angiogenesis. The integrin antagonist activity of the compounds of the present invention is demonstrated using assays which measure the binding of a specific integrin to a native ligand, for example, using the ELISA assay described below for the binding of vitronectin to the $\alpha_v\beta_3$ receptor.

The compounds of the present invention possess selectivity for the $\alpha_v\beta_3$ receptor relative to the GPIIb/IIIa receptor as demonstrated by their lack of

activity in standard assays of platelet aggregation, such as the platelet aggregation assay described below.

One of the major roles of integrins *in vivo* is to mediate cellular interactions with adjacent cells. Cell based adhesion assays can be used to mimic these interactions *in vitro*. A cell based assay is more representative of the *in vivo* situation than an ELISA since the receptor is maintained in membranes in the native state. The compounds of the present invention have activity in cell-based assays of adhesion, for example as demonstrated in using the cell adhesion assays described below.

The compounds of Formula I of the present invention may be useful for the treatment or prevention of other diseases which involve cell adhesion processes, including, but not limited to, osteoporosis, rheumatoid arthritis, autoimmune disorders, bone degradation, rheumatoid arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation, septic shock, psoriasis, eczema, contact dermatitis, osteoarthritis, atherosclerosis, metastasis, wound healing, inflammatory bowel disease and other angiogenic disorders.

The compounds of Formula I have the ability to suppress/inhibit angiogenesis *in vivo*, for example, as demonstrated using animal models of ocular neovascularization.

The compounds provided by this invention are also useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit integrin-ligand binding. These may be provided in a commercial kit comprising a compound of this invention.

As used herein "µg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "µL" denotes

microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "μM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma" stands for the Sigma-Aldrich Corp. of St. Louis, MO.

The utility of the compounds of the present invention may be assessed by testing in one or more of the following assays as described in detail below: Purified $\alpha_v\beta_3$ (human placenta) - Vitronectin ELISA, $\alpha_v\beta_3$-Vitronectin Binding Assay, Human Aortic Smooth Muscle Cell Migration Assay, In Vivo Angiogenesis Model, Pig Restenosis Model, Mouse Retinopathy Model. A compound of the present invention is considered to be active if it has an IC_{50} or K_i value of less than about 10 μM for the inhibition of $\alpha_v\beta_3$-Vitronectin Binding Assay, with compounds preferably having K_i values of less than about 0.1 μM. Compounds of the present invention are active in the $\alpha_v\beta_3$-Vitronectin Binding Assay as well as in cell-based assays of integrin adhesion mediated by the $\alpha_v\beta_3$-receptor.

Purified $\alpha_v\beta_3$ (human placenta) - Vitronectin ELISA

The $\alpha_v\beta_3$ receptor was isolated from human placental extracts prepared using octylglucoside. The extracts were passed over an affinity column composed of anti-$\alpha_v\beta_3$ monoclonal antibody (LM609) to Affigel. The column was subsequently washed extensively at pH 7 and pH 4.5 followed by elution at pH 3. The resulting sample was concentrated by wheat germ agglutinin chromatography to provide gave two bands on SDS gel which were confirmed as $\alpha_v\beta_3$ by western blotting.

Affinity purified protein was diluted at different levels and plated to 96 well plates. ELISA was performed using fixed concentration of biotinylated vitronectin (approximately 80 nM/well). This receptor preparation contains the $\alpha_v\beta_3$ with no detectable levels

of $\alpha_v\beta_5$ according to the gel ($\alpha_v\beta_3$) and according to effects of blocking antibodies for the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ in the ELISA.

A submaximal concentration of biotinylated vitronectin was selected based on conc. response curve with fixed receptor conc. and variable concentrations of biotinylated vitronectin.

$\alpha_v\beta_3$-Vitronectin Binding Assay

The purified receptor is diluted with coating buffer (20 mM Tris HCl, 150 mM NaCl, 2.0 mM $CaCl_2$, 1.0 mM $MgCl_2 \cdot 6H_2O$, 1.0 mM $MnCl_2 \cdot 4H_2O$) and coated (100 µL/well) on Costar (3590) high capacity binding plates overnight at 4°C. The coating solution is discarded and the plates washed once with blocking/binding buffer (B/B buffer, 50 mM Tris HCl, 100 mM NaCl, 2.0 mM $CaCl_2$,1.0 mM $MgCl_2 \cdot 6H_2O$,1.0 mM $MnCl_2 \cdot 4H_2O$). Receptor is then blocked (200 µL/well) with 3.5% BSA in B/B buffer for 2 hours at room temperature. After washing once with 1.0% BSA in B/B buffer, biotinylated vitronectin (100 µL) and either inhibitor (11 µL) or B/B buffer w/1.0% BSA (11 µL)is added to each well. The plates are incubated 2 hours at room temperature. The plates are washed twice with B/B buffer and incubated 1 hour at room temperature with anti-biotin alkaline phosphatase (100 µL/well) in B/B buffer containing 1.0% BSA. The plates are washed twice with B/B buffer and alkaline phosphatase substrate (100 µL) is added. Color is developed at room temperature. Color development is stopped by addition of 2N NaOH (25 µL/well) and absorbance is read at 405 nm. The IC_{50} is the concentration of test substance needed to block 50% of the vitronectin binding to the receptor.

Integrin Cell-Based Adhesion Assays

In the adhesion assays, a 96 well plate was coated with the ligand (i.e., fibrinogen) and incubated

overnight at 4° C. The following day, the cells were harvested, washed and loaded with a fluorescent dye. Compounds and cells were added together and then were immediately added to the coated plate. After incubation, loose cells are removed from the plate, and the plate (with adherent cells) is counted on a fluorometer. The ability of test compounds to inhibit cell adhesion by 50% is given by the IC_{50} value and represents a measure of potency of inhibition of integrin mediated binding. Compounds were tested for their ability to block cell adhesion using assays specific for $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_5\beta_1$ integrin interactions.

Platelet Aggregation Assay

Venous blood was obtained from anesthetized mongrel dogs or from healthy human donors who were drug- and aspirin-free for at least two weeks prior to blood collection. Blood was collected into citrated Vacutainer tubes. The blood was centrifuged for 15 minutes at 150 x g (850 RPM in a Sorvall RT6000 Tabletop Centrifuge with H-1000 B rotor) at room temperature, and platelet-rich plasma (PRP) was removed. The remaining blood was centrifuged for 15 minutes at 1500 x g (26,780 RPM) at room temperature, and platelet-poor plasma (PPP) was removed. Samples were assayed on a PAP-4 Platelet Aggregation Profiler, using PPP as the blank (100% transmittance). 200 µL of PRP (5×10^8 platelets/mL) were added to each micro test tube, and transmittance was set to 0%. 20 µL of ADP (10 µM) was added to each tube, and the aggregation profiles were plotted (% transmittance versus time). Test agent (20 µL) was added at different concentrations prior to the addition of the platelet agonist. Results are expressed as % inhibition of agonist-induced platelet aggregation.

Human Aortic Smooth Muscle Cell Migration Assay

A method for assessing $\alpha_v\beta_3$-mediated smooth muscle cell migration and agents which inhibit $\alpha_v\beta_3$-mediated smooth muscle cell migration is described in Liaw et al., *J. Clin. Invest.* (1995) 95: 713-724).

In Vivo Angiogenesis Model

A quantitative method for assessing angiogenesis and antiangiogenic agents is described in Passaniti et al., *Laboratory Investigation* (1992) 67: 519-528

Pig Restenosis Model

A method for assessing restenosis and agents which inhibit restenosis is described in Schwartz et al., *J. Am. College of Cardiology* (1992) 19: 267-274.

Mouse Retinopathy Model

A method for assessing retinopathy and agents which inhibit retinopathy is described in Smith et al., *Invest. Ophthal. & Visual Science* (1994) 35: 101-111.

Dosage and Formulation

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action, the $\alpha_v\beta_3$ integrin, in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents, such as a antiplatelet agent such as aspirin, piroxicam, or ticlopidine which are agonist-specific, or an anti-coagulant such as warfarin or heparin, or a thrombin inhibitor such as a boropeptide, hirudin or argatroban, or a thrombolytic agent such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof. The compounds of the invention, or compounds of the invention in combination with other

therapeutic agents, can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage of the novel cyclic compounds of this invention administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. A daily dosage of active ingredient can be expected to be about 0.001 to 10 milligrams per kilogram of body weight.

Dosage forms (compositions suitable for administration) contain from about 0.1 milligram to about 100 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet

from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 10 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive

displacement pump into gelatin to form soft gelatin capsules containing 10 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 10 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

The combination products of this invention, such as the novel $\alpha_v\beta_3$ antagonist compounds of this invention in combination with an anti-coagulant agent such as warfarin or heparin, or an anti-platelet agent such as aspirin, piroxicam or ticlopidine, or a thrombin inhibitor such as a boropeptide, hirudin or argatroban, or a thrombolytic agent such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof, can be in any dosage form, such as those described above, and can also be administered in various ways, as described above.

In a preferred embodiment, the combination products of the invention are formulated together, in a single dosage form (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the combination products are not formulated together in a single dosage form, the $\alpha_v\beta_3$ antagonist compounds of this invention and the anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent may be administered at the same time (that is, together), or in any order, for example the compounds of this invention are administered first, followed by

administration of the anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent. When not administered at the same time, preferably the administration of the compound of this invention and any anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent occurs less than about one hour apart, more preferably less than about 30 minutes apart, even more preferably less than about 15 minutes apart, and most preferably less than about 5 minutes apart. Preferably, administration of the combination products of the invention is oral. The terms oral agent, oral inhibitor, oral compound, or the like, as used herein, denote compounds which may be orally administered. Although it is preferable that the $\alpha_v\beta_3$ antagonist compounds of this invention and the anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent are both administered in the same fashion (that is, for example, both orally), if desired, they may each be administered in different fashions (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously). The dosage of the combination products of the invention may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

As discussed above, where two or more of the foregoing therapeutic agents are combined or co-administered with the compounds of this invention, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced

relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect which would be obtained as a result of addition of further agents in accordance with the present invention.

Particularly when provided as a single dosage form, the potential exists for a chemical interaction between the combined active ingredients (for example, a novel compound of this invention and an anti-coagulant such as warfarin or heparin, or a novel compound of this invention and an anti-platelet agent such as aspirin, piroxicam or ticlopidine, or a novel compound of this invention and a thrombin inhibitor such as a boropeptide, hirudin or argatroban, or a novel compound of this invention and a thrombolytic agent such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof). For this reason, the preferred dosage forms of the combination products of this invention are formulated such that although the active ingredients are combined in a single dosage form, the physical contact between the active ingredients is minimized (that is, reduced).

In order to minimize contact, one embodiment of this invention where the product is orally administered provides for a combination product wherein one active ingredient is enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. Another embodiment of this invention where oral administration is desired provides for a combination product wherein one of the active ingredients is coated with a sustained-release material which effects a sustained-release throughout the

gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

Dosage forms of the combination products of the present invention wherein one active ingredient is enteric coated can be in the form of tablets such that the enteric coated component and the other active ingredient are blended together and then compressed into a tablet or such that the enteric coated component is compressed into one tablet layer and the other active ingredient is compressed into an additional layer. Optionally, in order to further separate the two layers, one or more placebo layers may be present such that the placebo layer is between the layers of active ingredients. In addition, dosage forms of the present invention can be in the form of capsules wherein one active ingredient is compressed into a tablet or in the form of a plurality of microtablets, particles, granules or non-perils, which are then enteric coated. These enteric coated microtablets, particles, granules or non-perils are then placed into a capsule or compressed into a capsule along with a granulation of the other active ingredient.

These as well as other ways of minimizing contact between the components of combination products of the

present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Pharmaceutical kits useful in, for example, the inhibition of thrombus formation, the prevention of blood clots, and/or the treatment of thromboembolic disorders, which comprise a therapeutically effective amount of a compound according to the method of the present invention along with a therapeutically effective amount of an anti-coagulant agent such as warfarin or heparin, or an antiplatelet agent such as aspirin, piroxicam or ticlopidine, or a thrombin inhibitor such as a boropeptide, hirudin or argatroban, or a thrombolytic agent such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof, in one or more sterile containers, are also within the ambit of the present invention. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. The sterile containers of materials may comprise separate containers, or one or more multi-part containers, as exemplified by the UNIVIAL™ two-part container (available from Abbott Labs, Chicago, Illinois), as desired. The compounds according to the method of the invention and the anti-coagulant agent, anti-platelet agent, thrombin inhibitor, thrombolytic agent, and/or combinations thereof, may be separate, or combined into a single dosage form as described above. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily apparent to those

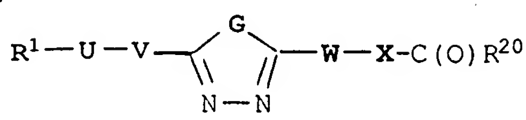
skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

Claims

What is claimed is:

1. A compound of the formula

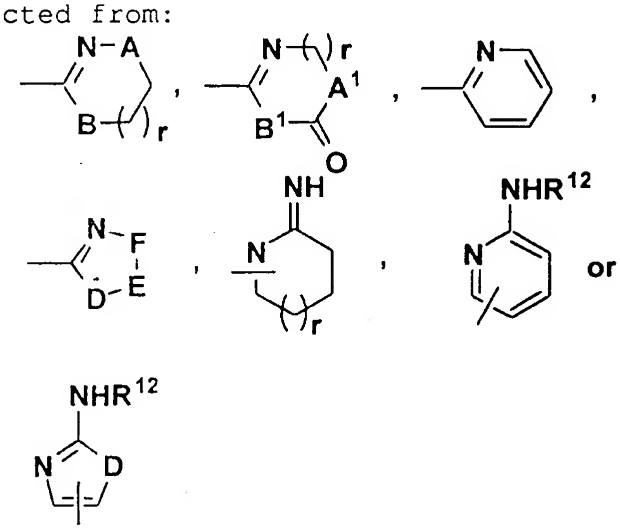
wherein:



(I)

including their enantiomeric, diastereomeric, pharmaceutically acceptable salt or prodrug forms thereof wherein:

R^1 is selected from:



A and B are independently CH_2, O or $-N(R^{12})-$;

A^1 and B^1 are independently CH_2 or $-N(R^{10})-$;

D is NH, O, or S;

E-F is $-C(R^2)=C(R^3)-$, $-N=C(R^2)-$, $-C(R^2)=N-$, $-N=N-$, or $-CH(R^2)CH(R^3)-$;

G is selected from O or S;

R^2 and R^3 are independently selected from: H, C_1-C_4 alkoxy, $NR^{11}R^{12}$, $=NR^{12}$, halogen, NO_2, CN, CF_3, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_7 cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, or C_7-C_{11} arylcarbonyl;

alternatively, R^2 and R^3 can be taken together to be a 5-7 membered carbocyclic or 5-7 membered heterocyclic ring system, said carbocyclic or heterocyclic ring being substituted with 0-2 R^7;

U is selected from:

$-(CH_2)_n-$,

$-(CH_2)_nN(R^{12})(CH_2)_m-$,

$-(CH_2)_nNHNH(CH_2)_m-$,

$-N(R^{10})C(=O)-$, or

$-C(=O)N(R^{10})-$;

V is selected from:

$-(CH_2)_n-$,

$-(C_1-C_6$ alkylene$)-Q-$, substituted with 0-3 groups independently selected from R^{13},

$-(C_2-C_7$ alkenylene$)-Q-$, substituted with 0-3 groups independently selected from R^{13},

$-(C_2-C_7$ alkynylene$)-Q-$, substituted with 0-3 groups independently selected from R^{13},

-(phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R^{13},

-(piperidinyl)-Q-, said piperidinyl substituted with 0-2 groups independently selected from R^{13},

-(pyridyl)-Q-, said pyridyl substituted with 0-2 groups independently selected from R^{13}, or

-(pyridazinyl)-Q-, said pyridazinyl substituted with 0-2 groups independently selected from R^{13} or R^7;

Q is selected from:

$-(CH_2)_n-$,

$-(CH_2)_nO(CH_2)_m-$,

$-(CH_2)_nN(R^{12})(CH_2)_m-$,

$-N(R^{10})C(=O)-$, or

$-C(=O)N(R^{10})-$;

W is selected from:

$-(CH_2)_qC(=O)N(R^{10})-$, $-SCH_2C(=O)N(R^{10})-$, or

$-C(=O)-N(R^{10})-(CH_2)_q-$;

X is selected from:

$-(CH_2)_q-CH(R^8)-CH(R^9)-$, $-(CH_2)_q-CH(CH_2R^9)-$ or $-CH_2-$;

R^5 is selected from: H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_7-C_{14} bicycloalkyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, $-N(R^{11})R^{12}$; halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, morpholinyl or pyridinyl;

R^6 is selected from:

H, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, nitro, C_1-C_6 alkylcarbonyl, $-N(R^{11})R^{12}$, cyano, halo, $-S(O)mR^{10}$, CO_2R^{10}, OR^{10},

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl, or

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, isoxazolinyl, isoxazolyl, or morpholinyl;

R^7 is selected from:

H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{11})R^{12}$, cyano, halo, CO_2R^{10}, OR^{10};

R^8 is selected from:

$CONR^{10}R^{11}$, $-CO_2R^{10}$,

C_1-C_{10} alkyl, substituted with 0-3 R^6,

C_2-C_{10} alkenyl, substituted with 0-3 R^6,

C_2-C_{10} alkynyl, substituted with 0-3 R^6,

C_3-C_8 cycloalkyl, substituted with 0-3 R^6,

C_5-C_6 cycloalkenyl, substituted with 0-3 R^6, aryl, substituted with 0-3 R^6, a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, isoxazolinyl, isoxazolyl or morpholinyl;

R^9 is selected from: H, hydroxy, C_1-C_{10} alkoxy, nitro, $N(R^{10})R^{11}$, $-N(R^{16})R^{17}$, C_1-C_{10} alkyl substituted with 0-3 R^6, aryl substituted with 0-3 R^6, heteroaryl substituted with 0-3 R^6 or C_1-C_{10} alkylcarbonyl;

R^{10} is selected from H or C_1-C_{10} alkyl substituted with 0-2 R^5;

R^{11} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_3-C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantylmethyl, or C_1-C_{10} alkyl substituted with 0-2 R^5;

alternatively, R^{10} and R^{11} when both are substituents on the same nitrogen atom (as in $-NR^{10}R^{11}$) can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from: 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl; said heterocycle being optionally substituted with 1-3 groups selected from: C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6 alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_7-C_{11} arylalkoxycarbonyl, C_1-C_6 alkylsulfonyl or C_6-C_{10} arylsulfonyl;

R^{12} is selected from:

H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylsulfonyl, aryl(C_1-C_4 alkyl)sulfonyl, arylsulfonyl, aryl, heteroarylcarbonyl, or heteroarylalkylcarbonyl, wherein said aryl groups are substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{13} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^{10} or $-C(=O)N(R^{10})R^{11}$;

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,

$-C(=O)-R^{18b}$,

$-SO_2-R^{18a}$,

$-SO_2-N(18^{b})_2$;

R^{17} is selected from H or C_1-C_4 alkyl;

R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},

C_2-C_8 alkenyl substituted with 0-2 R^{19},

C_2-C_8 alkynyl substituted with 0-2 R^{19},

C_3-C_8 cycloalkyl substituted with 0-2 R^{19},

aryl substituted with 0-4 R^{19},

aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, isoxazolyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl,

thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, isoxazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from: H, halogen, CF_3, CN, NO_2, $NR^{11}R^{12}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

R^{20} is selected from:

hydroxy;

C_1 to C_{10} alkoxy;

methylcarbonyloxymethoxy-,

ethylcarbonyloxymethoxy-,

t-butylcarbonyloxymethoxy-,

cyclohexylcarbonyloxymethoxy-,

1-(methylcarbonyloxy)ethoxy-,

1-(ethylcarbonyloxy)ethoxy-,

1-(t-butylcarbonyloxy)ethoxy-,

1-(cyclohexylcarbonyloxy)ethoxy-,

i-propyloxycarbonyloxymethoxy-,

t-butyloxycarbonyloxymethoxy-,

1-(i-propyloxycarbonyloxy)ethoxy-,

1-(cyclohexyloxycarbonyloxy)ethoxy-,

1-(*t*-butyloxycarbonyloxy)ethoxy-,

dimethylaminoethoxy-,

diethylaminoethoxy-,

(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-,

(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-,

(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-,
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-,

R^{21} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11}, cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^5;

m is 0-2;

n is 0-2;

p is 0-2;

q is 0-1; and

r is 0-2;

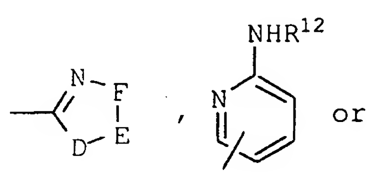
with the following provisos:

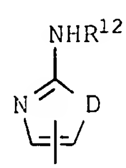
(1) n, m and q are chosen such that the number of atoms connecting R^1 and Y is in the range of 8-14; and

(2) when V is -(phenyl)-Q-, then either: U is not a direct bond (i.e., U is not $-(CH_2)_n-$ where n = 0) or Q is not a direct bond (i.e., Q is not $-(CH_2)_n-$ where n = 0).

Claim 2 is a compound of claim 1 wherein

R^1 is





; and

V is selected from:

$-(CH_2)_n-$,

-(C_1-C_6 alkylene)-Q-, substituted with 0-3 groups independently selected from R^{13},

-(C_2-C_7 alkenylene)-Q-, substituted with 0-3 groups independently selected from R^{13},

-(C_2-C_7 alkynylene)-Q-, substituted with 0-3 groups independently selected from R^{13},

-(phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R^{13},

-(pyridyl)-Q-, said pyridyl substituted with 0-2 groups independently selected from R^{13}, or

-(pyridazinyl)-Q-, said pyridazinyl substituted with 0-2 groups independently selected from R^{13} or R^7;

3. Claim 3 is a compound of claim 2 selected from the group consisting of:

2(S)-Phenylsulfonylamino-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acetyl]aminopropionic acid

2(S)-(3-methylphenylsulfonyl)amino-3-[2-[2-[3-[(N-imidazolin-2-yl)amino]propyl]-1,3,4-thiadiazol-5-yl]acetyl]aminopropionic acid

2(S)-Benzyloxycarbonylamino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-(2,4,6-Trimethylphenylsulfonyl)amino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-(1-Naphthalenesulfonyl)amino-3-[[2-[4-[N-(pyridin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-Benzyloxycarbonylamino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-(2,4,6-Trimethylphenylsulfonyl)amino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

2(S)-(1-Naphthalenesulfonyl)amino-3-[[2-[4-[(N-imidazolin-2-yl)amino]butyl]-1,3,4-thiadiazol-5-yl]carbonyl]aminopropionic acid TFA salt

4. A pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt from thereof.

5. A pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of Claim 2 or a pharmaceutically acceptable salt form thereof.

6. A pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of Claim 3 or a pharmaceutically acceptable salt form thereof.

7. A method in inhibiting the aggregation of blood platelets which comprises administering to a host in need of such inhibition a therapeutically effective amount of a compound of Claim 1.

8. A method of inhibiting the aggregation of blood platelets which comprises administering to a host in need of such inhibition a therapeutically effective amount of a compound of Claim 2.

9. A method of inhibiting the aggregation of blood platelets which comprises administering to a host in need of such inhibition a therapeutically effective amount of a compound of Claim 3.

10. A method of treating thromboembolic disorders selected from thrombus or embolus formation, harmful platelet aggrgation, reocclusion following thrombolysis, reperfusion injury, restenosis, atherosclerosis, stroke, myocardial infarction, and unstable angina, which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 1.

11. A method of treating thromboembolic disorders selected from thrombus or embolus formation, harmful platelet aggregation, reocclusion following thrombolysis, reperfusion injury, restenosis, atherosclerosis, stroke, myocardial infarction, and unstable angina, which comprises administering to a host in need of such treatment a threapeutically effective amount of a compound of Claim 2.

12. A method of treating thromboembolic disorders selected from thrombus or embolus formation, harmful platelet aggregaion, reocclusion following thrombolysis, reperfusion injury, restenosis, atherosclerosis, stroke myocardial infarction, and unstable angina, which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 3.

INTERNATIONAL SEARCH REPORT

Interr. .al Application No
PCT/US 98/24179

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D417/12 A61K31/41 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 668 159 A (CONFALONE PASQUALE NICHOLAS ET AL) 16 September 1997 see page 66, column 67; claim 1 -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 1999	12. 03.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT	International application No. PCT/US 98/24179

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/24179

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5668159 A	16-09-1997	NONE	